The attached Medwatch reports do not contain any potential follow- up to initial reports received through telephone report.

MedWatch Forms (USA)

MED WATCH

Aventis Pharma, Inc.

US

200110085
UF to strepon a

Page	1	of 3	

A Patient in	nformation						FDA Jue Or
Patient identifier	2. Age at time		3. Sex	4. Weight	C. Suspect med	ication(s)	
Æ	of event	29 yrs	1		1. Name (give labeled strength		
	or Date		female	or lbs	# TELLINOMIDE ()	ARAVA) Tablets	
in confidence	Date 04/1	13/1971	male	KGS	s #2		•
B. Adverse	event or prod	uct proble	em		2. Dose, frequency & route use	id 3. Therapy dates	(Éuro nown Give duration)
1. Adverse even			olem (e.g., defect	s/ma functions	#1 20 MG/DAY PO	To read again	on: 3 months
2. Outcomes attributed	to adverse event		(0.9., 00.00.	J/1110 10110113 3			5
(check ail that apply)	3/2001	disabi	,		1 #2 2	#2	
death	medica:	-	nital ariomaly		4. Diagnosis for use (indication)		Event abated after use stopped or dose reduced
de-threatening		perma	ed intervention ic p nent impairment/d		ADULT ONSET ST	ILL'S DISEASE	yes ind doesn't
nespharzation 	- initial or prolonged	other:			6 1 - 1 - 1		apply 12 yes no doesn't
3 Date of	/22/2000	4. Date of			6. Lot#(if known)	7. Exp. date (if known)	yes no doesn't
event 12,	/??/2000	this repo	on 01/17/2	2001	P1	.#1 'ε :	Event reappeared after reintroduction
Describe event or pro	blem				#2	1/2	1 yes no doesn't
Front (N	,				9. NDC # - for product problems o	nly (if known)	apply
	ature of Eve			rigin	Ħ	#2 #	yes no doesn't
	MINANT HEPA!	FIC FAIL	URE Repo	rter	10. Concomitant medical product	s and therapy dates (exclude treat	apply mant of wearth
•	TAL)				ATOVAQUONE		
	REASED SGOT				AZITHROMYCIN		•
	REASED SGPT				CALCIUM		•
	REASED ALKAI				METHYLPREDNISOLONE	(MEDROL) *	:
	SPHATASE 153				G. All manufacture	ers	
	REASED BILIR				1. Contact office - name/address (2. Phone number
	SEMINATED IN		AR Repor	rter	Aventis Pharma, Inc.		(816) 966-5000
	ULATION (FA				10236 Marion Park Dr	ive	3. Report source
	-RECTAL HER		Repor	ter	Kansas City, KO		(check all that apply)
	TIONS SUGGE			1	64137		foreign
HERP	ETIC HEPATI	TIS		į			study
				į	1		literature
	: Initial r			;			consumer
	ting case f					With the second second	health
	ysician and				4. Date received by manufacturer income.	5. (AINDA# 20-905	professional
female pa	tient who in	nitiated	therapy w	ith *	01/08/2001		user facility
Relevant tests/laborator	y data, including dates				F. # IMO perhaps ! #	# C/I	company representative
				'	6. If IND, protocol#	PLA#	distributor
				1		pre-1938 j yes	other:
					7. Type of report (check all that apply)	OTC	
					5-day 🔀 15-day	product yes	
					1 5-0ay //, 15-day	8. Adverse event term(s)	
					10-day periodic	REPATIC FAILURE,	ASPARTATE
					Initial F follow-up # 1	AMINOTRANSFERASE	
Other mievant hietoni in	cluding negovieties	marina .				ALANINE AMINOTRAN	SPERASE
Other relevant history, in smoking and aconol use	nepatic renal dystunction	ruicai conditiona on, etc.)	rije gi, altergies, race	, pregnancy 	9. Mfr report number	INCREASED, BLOOD	
30/W = 015				11	200110085US	PHOSPHATASE NOS II	NCREASED, *
	T STILL'S D				E. Initial reporter		
	RESSED, MAR			LE	Name, address & phone #		
	USE, alcoho	l use, d	rug abuse		ROBERT SANDS Dr		
history				f 1	111 GROSSMAN DR		DSS
PCP PROPHY	LAXIS			1 1			U

JOINT PAINS

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event tem completed on continuation pages

2. Health professional? 3. Occupation .yes no

UNITED STATES 481-849-2265

JAN 2 2 2011 4 Initial reporter also sent report to FDA



A.1. Patient Identifier

MED WATCH

G.9. Mfr. report number

Page 2 or 3

8 5. Doscribe event or problem

[continuation:] Arava (leflunomide) 20 mg daily (unknown if loading dose was given) approximately 2-3 months ago for adult onset Still's disease. Significant medical history includes very difficult adult onset Still's disease treated with many immunosuppressive medications, immunosuppressed, marijuana use and possible alcohol abuse. Concomitant medications include atovaquone, asithromycin, calcium, methylprednisolone, multivitamins, oxycodone/acetaminophen and influximab. The patient's liver enzymes were markedly elevated in early Dec 2000. At some point it was discovered that her dose of atovaquone (patient was not HIV positive) was three times the prescribed dose due to a medication error. Cholestyramine was initiated on 10 Dec, but the patient only took 4g three times a day and did not complete the course. She did not return for repeat lab tests on 21 Dec. Jaundice was noted on 24 Dec. but the patient refused hospital admission. The patient was admitted to the hospital on 27 Dec and had a rapidly progressive downhill course. On admission SGCT 1574, SGPT 1679, Alk Phos 153, Amylase 103, Bilirubin 31, Lipase 426 and Albumin 2.4. Cholestyramine was re-started. The patient developed disseminated intravascular coagulapathy and clotted off the supply to the liver. PTT 123 (22-34), PT 32 (11-13), INR went from 1.03 to 5 (dates unknown). Toxicology screen was positive only for opiates (she had received oxycodone/acetaminophen for joint pain). Blood cultures were negative; urine and sputum were positive for yeast. Peri-rectal herpetic eruptions were noted which suggested the possibility of herpetic hepatitis. Liver biopsy was not performed as it was considered too dangerous. Hepatitis A, B and C were negative. At the end of Dec (date unknown) SGOT and SGPT were in the "2000 range", Creatinine 2.1, CO2 8.0 and Albumin was 1.0. She was transferred to the clinic for evaluation for a liver transplant but died on 3-Jan-2001 of fulminant hepatic failure. The reporter will request an autopsy. The reporter indicated that the hepatic toxicity could have been related to Arava, liver compromise due to alcohol use and other medications, immunosuppression, herpetic hepatitis, the patient's underlying Still's disease or a combination of all factors. Further information is requested.

ddendum for 08-Jan-01: Follow-up information received from Lab Corp.via a physician. Demographics were provided. Ysician reported that the patient was transferred to Lahey Clinic for transplant. The reporting physician saw the atient for 2 days prior to transfer and recalled that the patient was treated with "pressors to maintain blood pressure" (nos). Work-up for infection was negative. Three liver ultrasounds were done, however, reporter did not have results. No further information was provided.

Addendum for 16-Jan-01: Follow-up information was received from a sales representative. The patient was number 1 on the list in New England for a liver transplant, but died before the transplant could be performed. Autopsy was not performed. The physician indicated that after "reviewing all the data, he does not believe the hepatic failure was due to Arava", however, he gave no other specific alternative explanation

Event (Dx) FULMINANT HEPATIC FAILURE	Serious YES	Dechal NO	Rechal NA	Rpt.Causality Unlikely	Alternative Emplanation possibly associated with	
(FATAL)				-	concomitant drug(s)	
(Sx) INCREASED SGOT >2000						
(Sx) INCREASED SGPT >2000						
(Sx) INCREASED ALKALINE						
PHOSPHATASE 153						
(Sx) INCREASED BILIRUBIN 31						
(Dx) DISSEMINATED INTRAVASULAR	YES	NO	NA		possibly associated with	
COAGULATION (FATAL)					concomitant drug(s)	OSS
'Dx) PERI-RECTAL HERPETIC	NO	NO	NA		underlying/concomitant illness	🗸 📞
PTIONS SUGGESTING HERPETIC						M 9 9 30
PATITIS					JA	N 2 2 700.



A.1. Patient Identifier

MED WATCH

A.E

G.9. Mfr. report number 20011008505

Page 3 of ,

B 5. Describe event or problem

[continuation:]

C.10. Concomitant medical products and therapy dates (exclude realment of event)

[continuation:] ERGOCALCIFEROL, ASCORBIC ACID, FOLIC ACID, THIAMINE HYDROCHLORIDE, RETINOL, RIBOFLAVIN, NICOTINAMIDE, PANTHENOL (MULTIVITAMINS)

PARACETAMOL, OXYCODONE HYDROCHLORIDE, OXYCODONE TEREPETHALATE (PERCOCET) INFLIXIMAB (REMICADE)

G.8. Adverse event term(s)

[continuation:] BLOOD BILIRUBIN INCREASED, DISSEMINATED INTRAVASCULAR COAGULATION, HERPES VIRAL INFECTION NOS

DSS

JAN 2 2 201

MedWatch Forms (USA)



TTT

Aventis Pharma, Inc.

Oomain Facsimile Approv Mir report # 20002091403	ed by Fo	A on 3/72/94
UF/Dist report 8		

A. Patient information C. S	
MED WATCH THE FDA MEDICAL PRODUCTS REPORTING PROGRAM Page 1 of 5	
ACD MARKET	UF/Dist raport 8

THE TOA WEDIC	AL PRODUCTS REPORT	NG PROGRAM		rage (or 5	1	
A. Patient	information			C. Suspect medic	cation(c)	FDA (J
1. Patient identifier	2. Age at time	3. Sex	4. Weight	Name (give labeled strength &	mfr/labeler if known	
TGB	of event: 51	yrs Semale	Ibs			
in confidence	Date of birth: UNK	male	or kgs	#2 LEFLUNOMIDE (A	RAVA) Tablet	•
B. Adverse	event or produc	t problem	,	2. Dose, frequency & route used		rapy dates (if unknown, give duration)
Adverse eve		roduct problem (e.g., defect	s/malfunctions			#o (or cost estimate)
Outcomes attribute	ed to adverse event		arrio il directoria	7		
(check all that apply	^{y)} /10/2000	disability		#2 20 MG/DAY PO 4. Diagnosis for use (indication)	#2	08/07/2000 to ??/??/2000
oeatri	(mortanytyr)	congenital anomaly required intervention to	oro: est	#1 RHEUMATOID ARTE	मा गाय	Event abated after use stop or dose reduced
ife-threateni	•	permanent impairment/o	damage			—— #1 ☐ yes ☐ no ⊠ doe:
hospitalization	on - initial or prolonged	other:		#2 RHEUMATOID ARTE		appi
Date of		4. Date of		6. Lot#(if known)	7. Exp. date (if kno	wn) yes no i does
event 0 (modeyyn)	9/05/2000	this report 01/08/	2001	<u> </u>	#1 	Event reappeared after reintroduction
Describe event or p	roblem	<u> </u>		M2	1/2	n yes no does
Event (Nature of Ever	n+1 n= 0		9. NDC#- for product problems or		apply
	UTE HEPATIC NE		rigin rtor	#1	#2	yes rold does
	CREASED ALT 60		T CALL	10. Concomitant medical products		xclude treatment of exent)
	CREASED AST 40			PREDNISONE	to Unknown	
•	CREASED BILIRU	-		PRADRISONE		
	CREASED ALKALI					
	OSPHATASE >140			G. All manufacture		
	UNDICE	•	ĺ	Contact office - name/address (8)	& mfring site for device	es) 2. Phone number
	VER NOS			Aventis Pharma, Inc.		(816) 966-5000
	CULOPAPULAR RA	SH Repor	rtor	10236 Marion Park Dr	ive	·
	ELECTASIS	Repor	1	Kansas City, MO		3. Report source (check all that apply)
	ver nos	Webot	· Car	64137		[foreign
	EURITIC PAIN					study
	CREASED COAGUL	OPATHY Repor	tor			literature
	CREASED PROTIN		. 031			consumer ⊠ health
	CELL APLASIA		+0=	4. Date received by manufacturer	5.	professional
• •	VER (104)	Repor		(moldayryr)	(A)NDA # 20	
		Mapor		12/29/2000	IND #	company
WANTE BEAUTIONS	story data, including dates			6. If IND, protocol #	PLA#	representative
					pre-1938	L_l distributor
				7. Type of report	i OTC	yes other
				(check all that apply)	product	[] yes
				5-day 🔯 15-day	8. Adverse event	(horm/e)
				10-day periodic		CROSIS, ALANINE
				Initial Sollow-up # 7	AMINOTRANS	FERASE INCREASED,
Other relevant history	y, including presidsting med	ical conditions (e.g., allergies, race	e. pregnancy	9. Mir. report number		AMINOTRANSFERASE
moking and alcohol i	use, hepatic/renal dysfunctio	in, etc.)	3 3 -01.	20002091403		BLOOD BILIRUBIN BLOOD ALKALINE *
NO MENTI	ON OF RELEVANT	DISEASE				
unk				E. Initial reporter		
			1	1. Name, address & phone #		
				GRISANTI MD UNITED STATES		
			:	ousten Stutes		
)		
DA		report does not constitut edical personnel, user fa		2. Health professional? 3. O	ccupation	, 4. Initial reporter also
		facturer or product cause		🗵 yes 🗀 no		ment report to FDA
Faculment of	contributed to the					esonunk

tem completed on continuation pages.

_	Health profe	esional?	Occupation	4. mitia/ reporter also
	∴ yes	L no	:	es no unik
			1 5001	· · · · · · · · · · · · · · · · · · ·



Domain Facsimile	Annough 604
Mir report #	Approved by FDA on 3723
20002091403	
UF/Dist report #	

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM Page 2 of 5 FOA Use Only A. Patient information C. Suspect medication(s) 2. Age at time of event: 1. Patient identifier 3. Sex 4. Weight 1. Name (give labeled strength & mfr/labeler, if known) TGB [female CELECOXIB (CELEBREX) ibs 13 or __ male in confidence kgs B. Adverse event or product problem 2. Dose, frequency & route used 3. Therapy dates (if unknown, give diration) tomo for best estimate)

7?/??/2000 to Unknown

7. **Therapy dates (if unknown)

**Therapy dates (if unknown) 1. Adverse event and/or 200 MG/DAY #3 Product problem (e.g., defects/malfunctions) 2. Outcomes attributed to adverse event (check all that apply) disability 4. Diagnosis for use (indication) congenital anomaly Event abated after use stopped death _ or dose reduced RHEUNATOID ARTHRITIS required intervention to prevent life-threatening #3 ___ yes ___ no __ doesn't permanent Impairment/damage hospitalization - initial or prolonged apply __ other: #4 ___ yes __ no __ doesn't 6. Lot # (if known) 7. Exp. date (if known) 3. Date of 4. Date of apply event (motteylyr) #3 Event reappeared after reintroduction 5. Describe event or problem #4 #3 yes no doesn't 9. NDC # - for product problems only (if known) apply #4 yes __ no __ doesn't 10. Concomitant medical products and therapy dates (exclude treatment of event) G. All manufacturers 1. Contact office - name/address (& mfmng site for devices) 2. Phone number 3. Report source (check all that apply) foreign study literature consumer health professional 4. Date received by manufacturer (mordeylyr) (A)NDA# user facility IND# 6. Relevant tests/shoratory data, including dates representative 6. # ND, protocol # PLA # ___ distributor pre-1938 yes other 7. Type of report (check all that apply) OTC yes product 5-day 15-day 8. Adverse event term(s) 10-day periodic ☐ Initial ☐ follow-up #_ Other relevant history, including prescripting medical conditions (e.g., allerges, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) 9. Mfr. report number E. Initial reporter 1. Name, address & phone # Submission of a report does not constitute an 2. Health professional? 3. Occupation 4. Initial reporter also admission that medical personnel, user facility, yes no ___ ves ___ no ___ unk

distributor, manufacturer or product caused or contributed to the event.
Item completed on continuation pages.

1001 2 0 2001



	A.1. Patient Identifier	G.9. Mfr. report number	
MED WATCH	TGB	20002091403	
			Page 3 of 5

B.2. Other outcome

medically important

B.5. Describe event or problem

[continuation:] (Dx) SEVERAL FEBRILE EPISODES Reporter

(Dx) DUODENAL ULCER Reporter

(SE) GASTROINTESTINAL BLEED

(SE) POOR NUTRITION

(Sx) ALBUMIN LOW

(Dx) PERFORATED ULCER

Reporter

(Dx) LEFT LOWER LOBE PNEUMONIA

Reporter

(Dx) PERITORITIS

Reporter

(Dx) SEPTIC SHOCK FATAL OUTCOME Reporter (Dx) DEHISCENCE

Reporter

Marrative: Initial report: This postmarketing case from US received from Lab Corp via physician + involves 51 yr old female who received Arava (leflunomide) 20 mg daily for rheumatoid arthritis (insidous synovitis + rheumatoid factor negative) beginning approx. 4-5 months ago. Not known if patient received loading dose of leflunomide. Medical history is not reported. Concomitant medication includes celecoxib. Reporter states approx. 05-Sep-00 pt. was hospitalized due to rash, fever, pleuritic pain, + jaundice. Rash + fever had started approximately 2 weeks prior to hospitalization. Leflunomide + celecoxib were discontinued at that time + she was prescribed cholestyramine 8 grams three times a day. Initially discharged from hospital after first admission but was subsequently readmitted on unknown date due to fever. During second hospitalization she was noted to have telectasis, abnormal liver function tests and increased protime (27). Diagnosis of acute hepatic necrosis was made. She was transferred to another facility for evaluation for liver transplant. Reporter's assessment of causal relationship is that it cannot be excluded.

Lab Data	Date not provided
ALT	600
AST	400
PROTIME	27.1
PTT	31.4
BILI	9.0
ALK PHOS	270
ALBUMIN	2.2

Add 25-Sep-00: Info. rec'd from reporter: Clinically stabilizing 21-Sept-00. LFTs + prothrombin time decreasing. "The patient doing better". 3 leflunomide plasma levels drawn, last being greater than 1. Reporter unsure MD will continue cholestyramine. As of 21-Aug-00, had not undergone liver transplant + scheduled for liver biopsy on 22-Sept-00. Had multiple CT scans and ultrasounds.

Add 2-Oct-00: MD was contacted + provided: Fever 104 F last weekend + blood count low. Not sure pathent was transfused. Liver biopsy scheduled 22-Sept-00 cancelled + reporter unsure biopsy took place. No info. in regards to the pathology of liver.

Add 6-Oct-00: Discharged Cleveland Clinic 29-Sep-00 + to be followed by primary MD. LFT's + CBC to be monitored. Reporter: liver biopsy showed inflammation. Awaiting results of bone marrow biopsy.

Add 11-Oct-00: Info. rec'd from MD. Liver biopsy showed centrilobular necrosis w/ portal inflammation + hepatic necrosis consistent w/ drug reaction. Pt. did not have liver transplant as Cleveland Clinic felt pt. had enough liver tissue left to regenerate. Bone marrow biopsy revealed red cell aplasia + treated w/ plasma products to correct low blood count. Highest transaminases recorded were >1000, alkaline phosphatase >1400 and bilirubin 17 (dates not provided). Bili. decreased to 12 + transaminases improving, still high. Had 10 day course of cholestyramine but leflunomide levels remain elevated. Concomitant drug celecoxib is suspect drug.



	A.1. Patient Identifier	G.S. Mfr. report number	
MED WATCH	TGB	200020914US	
			Pag∈ 4 of 5

B.5. Describe event or problem

[continuation:] ADD 25-OCT-00: F/U rec'd from nurse in MD's office. Pt. had several febrile episodes since discharge from Cleveland Clinic necessitating laboratory work as outpatient. Admitted to hospitatl for gastrointestianl bleed, week-end of 21-Oct-00. Reporter believes she was transfused, not confirmed by MD. Arava level 11-Oct-00, 2.7. Reporter believes she underwent 2 washout procedures. Had bone marrow + liver cultures (looking for tuberculosis) in Cleveland, awaiting results.

ADD 27-OCT-00: F/U via voice mail from Rheu. Sales Rep. provides albumin levels low (nos) + nutrition poor, not ingesting anything orally. Has duodenal ulcer.

ADD 31-OCT-00: Reporter rec'd werbal report: results of liver + bone marrow cultures neg. for TB.

ADD 08-NOV-00: Perforated ulcer + GI bleed approx. 26-Oct. Surgery done 27 or 28-Oct-00. Taking + retaining food orally. Developed left lower lobe pneumonia post-op (end Oct or beg. Nov). Pneumonia treated + resolving. Still jaundiced, liver functions improving: bili. = 14. Arava level 31-Oct = 0.7. Improving, out of bed.

ADD 13-NOV-00: Info. provides: Discharged 08-Nov-00 after successful surgery from GI bleed. After discharge, "incision opened and contents of stomach went into abdomen which led to peritonitis". Returned to hospital for emergency surgery. Went into septic shock + died 10-Nov-00.

Add 07-Dec-00: Arava do'd prior to 07-Sep-00 (first Questran rx). Rec'd for less than 1 month. Celebrax began approx. 2 weeks prior to 14-Jul-00. Rac'd 30 doses Questran over several weeks, level was 6. MD feels stress ulcer from steroid therapy, fever, debilitation, poor nutrition. Several bleeding sites found. Angiogram + attempt to thrombose left gastric artery, unsuccessful. Surgery to tie off bleeders. Arava level was 1. Fever returned w/ capering steroids. 2 days post discharge, returned in septic shock, dehiscence of pyloroplasty, + peritonitis Succumbed after surgery due to GI bleed and complications. MD assessed dehiscence due to hypoalbuinem.a + steroids. 2 biopsies: no evidence of chronic liver disease no fibrosis or cirrhosis. Imp. both biopsies: acute hepatitis w/ some necrosis. First bx Cleveland + MD felt she would recover. Hep-A, B, + C neg. No hx alcohol problem. Refractory fever during illness, treated w/ tylenol + steroids. Cultures neg. No autopsy done. MD: assesses hepatic necrosis caused by Arava. Celebrax may have contributed, or poss. combination.

ADD 13-Dec-00: MD assessed Arava as cause of hepatic necrosis. Added: gastro. + CC felt the same. Assessed Celebrax as not related to events.

ADD 29-Dec-00: MD from Cleveland reports he saw pt for 4 days during 11 days in CC. Bone marrow: hypercellular, no evidence of malignancy, some polyclonal plasmacytosis, erythroid hypoplasia. Biopsy: mild portal + lobular hepatitis, centrilobular hepatocyte necrosis.

	19-Sep	28-Seg
AST	334	238
ALT	675	585
ALK PHOS	284	426
BILI	13.1	16

CAUSALITY: possibily related due to temporal relationship.

Case edited due to space.

(Dm) ACUTE HEPATIC NECROSIS

Serious Dechal Rechal Rpt. Causality Alternative Explanation YES NA NA Possible

possibly associated with



	A.1. Patient identifier	G.9. Mfr. report number	
MED WATCH	TGB	200020914US	
			Page 5 of 5

B.6. Describe event or problem

[continuation:]

concomitant drug(s)

erinuacion:)					concomitant drug
INCREASED ALT 600					
INCREASED AST 400					
INCREASED BILIRUBIN 17					
INCREASED ALKALINE					
SPHATASE >1400					
JAUNDICE					
FEVER NOS					
MACULOPAPULAR RASH	TES	NA	NA	Possible	possibly associated with
,					concomitant drug(s)
ATELECTASIS	YES	NA	NA	Possible	underlying/concomitant illness
PEVER NOS					
PLEURITIC PAIN					
INCREASED COAGULOPATHY	YES	NA.	NA	Possible	underlying/concomitant illness
INCREASED PROTING 27					
RED CELL APLASIA	TES	NA	N/A		
FEVER (104)	YES	NA	NA.		underlying/concomitant illness
SEVERAL FEBRILE EPISODES	NO	NA	NA		underlying/concomitant illness
DUCCENAL ULCER	YES	NA	NA		possibly associated with
					concomitant drug(s)
CASTROINTESTINAL BLEED					
POOR NUTRITION					
ALBUMIN LOW					
PERFORATED ULCER	TES	NA	NA		possibly associated with
				•	concomitant drug(s)
LEFT LOWER LOBE PNEUMONIA	YES	NA	NO.		other known or suspected cause
PERITONITIS	YES	NA	NA		other known or suspected cause
SEPTIC SHOCK FATAL OUTCOME	TES	NA	NA		other known or suspected cause
DEHISCENCE	YES	NA	NA		other known or suspected cause
	INCREASED AST 400 INCREASED BILIRUBIN 17 INCREASED ALKALINE SPEATASE >1400 JAUNDICE FEVER NOS MACULOPAPULAR RASH ATELECTASIS FEVER NOS PLEURITIC PAIN INCREASED COAGULOPATHY INCREASED PROTIME 27 RED CELL APLASIA FEVER (104) SEVERAL FEBRILE EPISODES DUCUENAL ULCER GASTROINTESTINAL BLEED POOR NUTRITION ALBUMIN LOW PERFORATED ULCER LEFT LOWER LOBE PNEUMONIA PERITONITIS SEPTIC SHOCK FATAL OUTCOME	INCREASED ALT 600 INCREASED AST 400 INCREASED BILIRUBIN 17 INCREASED ALKALINE BPHATASE >1400 JAUNDICE FEVER NOS MACULOPAPULAR RASH ATELECTASIS FEVER NOS PLEURITIC PAIN INCREASED COAGULOPATHY INCREASED PROTIME 27 RED CELL APLASIA FEVER (104) SEVERAL FEBRILE EPISODES NO DUCCENAL ULCER GASTROINTESTINAL BLEED POOR NUTRITION ALBUMIN LOW PERFORATED ULCER LEFT LOWER LOBE PMEUMONIA PES SEPTIC SHOCK FATAL OUTCOME INCREASED ALTON	INCREASED ALT 600 INCREASED AST 400 INCREASED BILIRUBIN 17 INCREASED ALKALINE SPHATASE >1400 JAUNDICE FEVER NOS MACULOPAPULAR RASH ATELECTASIS FEVER NOS PLEURITIC PAIN INCREASED COAGULOPATHY INCREASED PROTIME 27 RED CELL APLASIA FEVER (104) SEVERAL FEBRILE EPISODES NO NA GASTROINTESTINAL BLEED POOR HUTRITION ALBUMIN LOW PERFORATED ULCER LEFT LOWER LOBE PMEUMONIA FES NA PERITONITIS SEPTIC SHOCK FATAL OUTCOME TES NA	INCREASED ALT 600 INCREASED AST 400 INCREASED BILIRUBIN 17 INCREASED ALKALINE SPHATASE >1400 JAUNDICE FEVER NOS MACULOPAPULAR RASH ATELECTASIS YES NA NA FEVER NOS PLEURITIC PAIN INCREASED COAGULOPATHY INCREASED COAGULOPATHY INCREASED PROTIME 27 RED CELL APLASIA FEVER (104) SEVERAL FEBRILE EPISODES NO NA NA GASTROINTESTINAL BLEED POOR HUTRITION ALBUMIN LOW PERFORATED ULCER TES NA NA LEFT LOWER LOBE PNEUMONIA YES NA NA PERITONITIS YES NA NA NA SEPTIC SHOCK FATAL OUTCOME TES NA	INCREASED ALT 600 INCREASED AST 400 INCREASED ALKALINE INCREASED ALKALINE SPEATASE > 1400 JAUNDICE FEVER NOS MACULOPAPULAR RASH ATELECTASIS FEVER NOS PLEURITIC PAIN INCREASED COAGULOPATHY INCREASED COAGULOPATHY INCREASED PROTIME 27 RED CELL APLASIA FEVER (104) SEVERAL FEBRILE EPISODES NO NA DUODENAL ULCER GASTROINTESTINAL BLEED POOR NUTRITION ALBUMIN LOW PERFORATED ULCER TES NA NA NA LEFT LOWER LOBE PNEUMONIA SES NA NA NA SEPTIC SHOCK FATAL OUTCOME TES NA NA NA SEPTIC SHOCK FATAL OUTCOME TES NA NA NA SEPTIC SHOCK FATAL OUTCOME TES NA NA NA

C.3. Therapy dates (if unknown, give duration) (mo/day/yt) (Suspect #1)

08/04/2000 to 08/06/2000 Duration: 3 days

G.S. Adverse event term(s)

[continuation:] PHOSPHATASE NOS INCREASED, JAUNDICE NOS, PYREXIA, RASH MACULO-PAPULAR, ATELECTASIS, PYREXIA, PLEURITIC PAIN, COAGULATION DISORDER NOS, PROTHROMBIN TIME PROLONGED, RED CELL APLASIA, PYREXIA, PYREXIA, DUODENAL ULCER, GASTROINTESTINAL HAEMORRHAGE NOS, MALNUTRITION NOS, BLOOD ALBUMIN DECREASED, INTESTINAL ULCER PERFORATION NOS, LOBAR PNEUMONIA NOS, PERITONITIS, SEPSIS NOS, WOUND DEHISCENCE

MedWatch Forms (USA)



3444-145-54
Approved by FDA on 3/22/9

MED	VVA	ICH
THE FDA MEDICAL	PRODUCTS PEPO	DTING DROCDAN

2. Age at time of event:

Patient information

BF

DA MEDICAL PRODUCTS REPORTING PROGRAM

53 yrs

3. Sex

⊠ female

4. Weight

Page 1 of 2		FDA √se
C. Suspect medic	ation(s)	
1. Name (give labeled strength of LEFLUNOMIDE (A		· · · · · · · · · · · · · · · · · · ·
#	KAVA) Tablets	
	RAVA) Tablets	
Dose, frequency & route used 100 MG QD PO	3. Therapy da	tes (if unknown, give duration)
100 MG QD PO		
2 100 MG QD PO	#2	
Diagnosis for use (indication) RHEUMATOID ARTH	IRITIS	Event abated after use stoppe or dose reduced
RHEUMATOID ARTH	RITIS	#1 yes rio doesn apply
Lot # (if known)	7. Exp. date (if known)	#2 yest rio doesn
	#1	8. Event reappeared after reintroduction
NOC# former at a state	#2	#1 yes rio desn'
NDC # - for product problems o		apply
Constitution	#2	anniu
Concomitant medical products LFASALAZINE (AZULF		reatment of events
SOPROSTOL (CYTOTEC		
EDNISONE	,	
6. All manufacture	re	
Contact office - name/address (8		2. Phone number
entis Pharma, Inc.		(816) 966-5000
236 Marion Park Dr.	ive	3. Report source
nsas City, MO 137		(check all that apply)
,	R 1 1 2000	foreign
Ar	1/ 1 + 2000	study
		J literature
		, health
ate received by manufacturer	5. (A)NDA # 20-905	professional
03/30/2000	1	user facility
IND, protocol #	IND#	company representative
, protocot #	PLA #	distributor
	pre-1938 y	es other
rpe of report check all that apply)	OTC ye	es
5-day	8. Adverse event termis	
10-day periodic		R, LIVER FUNCTION
Initiai follow-up #	TEST ABNORMAL,	BACK PAIN. LIVER
lfr. report number	FAILURE, COMA,	WEIGHT LOSS,
011168HMRI	TONGUE PAIN	
		·
Initial reporter		
ame, address & phone #		•
KY FYFFE MS. LAKEVIEW DRIVE SOU	TTU	
SHALL, TX 75672) t u	
TED STATES 903-938	-3049	
ealth professional? 3. O	ccupation 4	Initial reporter also sent report to FDA

1 :	Date on the		I —	or
	of birth: 07/1:	1/1946	male	kg
B. Adverse eve	nt or produ	ct proble	m	
1. Adverse event ar			lem (e.g., defect	s/malfunction
Outcomes attributed to ad (check all that apply)		[-]		
		disabil	•	
death	ay'yr)		nital anomaly	
∐ life-threatening		perma	ed intervention to nent impairment/o	prevent Iamage
hospitalization - in	itial or prolonged			•
3. Date of		4. Date of		
event 05/??	/1999	this repor	1 04/06/2	2000
5. Describe event or problem		(maraayiyi)		
	•			
Event (Natu	re of Eve	nt)	Dx Or	igin
(Dx) LOST I	ASTE BUDS		Repor	ter
(Overdose	1)			
(Dx) ELEVAT	ED LIVER F	ENZYMES	NOS Repor	ter
(Overdose	1)		-	
(Dx) BAD BA	CK ACHE		Repor	ter
(Overdose)			
(Dx) COMPLE	TE LIVER F	AILURE	Repor	ter
(Overdose			nepo1	CEI
(Sx) COMA	•			
(Dx) WEIGHT	1000		D	
(Overdose			Report	er
(Dx) TONGUE	•			
			Report	er
(Overdose)	,			
Narratina.	Padada3			
Narrative:			his	
postmarketi	ng case ir	om the C	S was rece	ived *
Relevant tests/laboratory dat	a, including dates			
				1
				1
Other relevant history, includ	ling presisting ma	lical conditio	/a a allerana	
smoking and alcohol use. he	patic/renal dysfunct	ion, etc.)	ite y., allergies, race	· pregnancy :
SMOKED			Į".	
SMOKER, nico	tine use			
			420	*
			APR I	2 200-1
				CULIJ

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages



	Y		
1	A.1. Patient identifier	G.9. Mfr. report number	T
TED WATCH	BF	200011168HMRI	
			Page 2 of 2

B.5. Describe event or problem

[continuation:] from a 53 year old consumer who reports that she was receiving Arava (leflunomide) 100mg for rheumatoid arthritis from Apr-99 until May-99 and experienced loss of taste buds. She discontinued the leflunomide and recovered from the event. At a later time in June or July of 1999, she saw her rheumatologist who recommended she resume therapy with Arava, 100mg once a day. She reports taking a total of 87 days at this dose. In approximately June she had liver function tests performed and was told that her liver enzymes were elevated (NOS) and she was instructed to continue to take Arava. On 12-Aug-99 she was seen because of a bad back ache located bilaterally in her kidney areas. On 13-Aug-99 she was hospitalized for "complete liver failure" and went into a coma. She also reports weight loss and tongue burning during this time. She was discharged on 21-Aug-99 and received lactulose until Feb-00. The patient states that in Feb-00 she underwent a liver biopsy which revealed her liver damage had resolved. The patient denies any previous liver problems and refused permission to contact her physician. Further information has been requested, however is not anticipated. Significant medical history includes smoking. Concomitant medications include sulfasalazine, misoprostol and prednisone. This report has not been substantiated by a healthcare professional.

Reporter assessment of the causal relationship between the adverse event and suspect drug:
[_] Possible [_] Unlikely [_] Unrelated
[_] Insufficient Data
If unlikely/unrelated, provide alternative explanation:
[_] Illness [_] Concomitant Drug [_] Other

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1) 04/??/1999 to 05/??/1999 Duration: 1 month

APR 1 1 2000

APR 12 2000

MedWatch Forms (USA)



THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

rion Roussel, Inc.

Domain Facsimile	
Mir report #	Approved by FDA on 3/22/94
199920773HMRI	
JF/Dist report #	

		FDA (
C. Suspect me	dication(s)	
1. Name (give labeled stren		
# LEFLUNOMIDE	(ARAVA) Tables	
#2		
2. Dose, frequency & route	J. The	rapy dates (if unknown, give duration)
#1 QD PO	#1 '	*
#2	-	
4. Diagnosis for use (indicati	00)	1
#1 RHEUAMTOID A		Event abated after use stored or dose reduced
		— #1 yes no oo doe.
#2		аррі
6. Lot#(if known)	7. Exp. date (if know	wn) #2 yes no _ does
#1	#1	B. Event reappeared after
#2	-	reintroduction
	#2	#1 ☐ yes ☐ no ☒ does
9. NDC # - for product problem		apph
#1	#2	#2 yes no does
10. Concomitant medical produ	icts and therapy dates (exc	clude treatment of event)
ALLOPURINOL		- 177
SULFAMETHOXAZOLE,	TRIMETHOPRIM (BACTRIM DS)
AMITRIPTYLINE HYDR	OCHLORIDE (ELA	VIL)
LISINOPRIL *		
G. All manufactu	rore	
. Contact office - name/addres		
Hoechst Marion Rou		2. Phone number (816) 966-5000
0236 Marion Park		(010)300-3000
Cansas City, MO		3. Report source
4137		(check all that apply)
,		foreign study
4,		
		literature
		consumer
Date received by manufacturer	5.	health professional
(M o/dryryr)	5. (A)NDA # 20-	professional
Date received by manufacturer moteryin 08/24/1999		professional 905 user facility
08/24/1999	(A)NDA # 20-	professional
08/24/1999	(A)NDA # 20-	professional go5 user facility company
08/24/1999 # ND, protocol #	(A)NDA # 20- IND # PLA #	professional gos user facility company representative
08/24/1999 # ND, protocol#	(A)NDA # 20- IND # PLA #	professional user facility company representative distributor yes other:
08/24/1999 # ND, protocol # Type of report (check all that apply)	(A)NDA # 20- IND # PLA # pre-1938	professional gos user facility company representative distributor
08/24/1999 # ND, protocol # Type of report (check all that apply)	(A)NDA # 20- IND # PLA # pre-1938 OTC product	professional gos user facility company representative distributor yes other:
68/24/1999 # ND, protocol # Type of report (check all that apply) 5-day 15-day	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse evers to	professional gos user facility company representative distributor yes other: yes
Type of report (check all that apply) 5-day 15-day periodic	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse evers to LIVER FAILU	professional go5
7 ND, protocol # Type of report (check all that apply) 5-day 15-day 10-day penodic	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA	professional go5
Type of report (check all that apply) 5-day 15-day penodic Initial follow-up #	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED,	professional go5 user facility company representative distributor yes other: yes prm(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN
Type of report (check all that apply) 5-day 15-day penodic Initial follow-up #	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED,	professional go5 user facility company representative distributor yes other: yes prm(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED,
Type of report (check all that apply) 5-day 15-day penodic Initial follow-up #	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED,	professional go5 user facility company representative distributor yes other: yes prm(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN
Type of report (check all that apply) 5-day 15-day penodic Initial follow-up #	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED,	professional go5 user facility company representative distributor yes other: yes prm(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED,
Type of report (check all that apply) 5-day 15-day 10-day penodic Initial follow-up # Wr. report number 9920773HMRI	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED,	professional go5 user facility company representative distributor yes other: yes prm(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED,
Type of report (check all that apply) 5-day 15-day 10-day penodic Initial follow-up # Wir. report number 9920773HMRI Initial reporter Iame, address & phone #	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED,	professional go5 user facility company representative distributor yes other: yes prof(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED, ION TEST ABNORMAL, *
No. protocol # Type of report (check all that apply) 5-day	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED, LIVER FUNCT:	professional go5 user facility company representative distributor yes other: yes prm(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED,
Type of report (check all that apply) 5-day 15-day 10-day penodic Initial follow-up # Wr. report number 9920773HMRI Initial reporter Iame, address & phone # cren Alexander MD ahoma City VA Meditical Intensive Cal	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED, LIVER FUNCT:	professional gos user facility company representative distributor other: yes em(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED, ION TEST ABNORMAL, =
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Type of report (check all that apply) 5-day 15-day 10-day penodic Initial follow-up # With report number 9920773HMRI Initial reporter ame, address & phone # Fren Alexander MD ahoma City VA Medical Intensive Can NE 13th Streer *	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED, LIVER FUNCT:	professional gos user facility company representative distributor other: yes em(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED, ION TEST ABNORMAL, =
Type of report (check all that apply) 5-day 15-day 10-day penodic Initial follow-up # Wir. report number 9920773HMRI Initial reporter fame, address & phone # Eren Alexander MD ahoma City VA Medical Intensive Can NE 13th Streer *	(A)NDA # 20- IND # PLA # pre-1938 OTC product 8. Adverse event to LIVER FAILU ENCEPHALOPA DECREASED, DECREASED, LIVER FUNCT:	professional gos user facility company representative distributor other: yes em(s) RE, ASCITES, JAUNDICE, THY, PROTHROMBIN THROMBOPLASTIN PROTHROMBIN DECREASED, ION TEST ABNORMAL, =

Patient identifier					
, ,	2. Age at time of event:	E E	1770	3. Sex	4. Weigi
	-r	25	yrs		ī
in confidence	Dam	04/02/	1944	⊠ male	or
B. Adverse	Of DEED:				_
1. Mada	event or pr				
Adverse even Outcomes attributed		Pro	oduct prob	lem (e.g., defe	cls/malfunct
(check all that apply)	to adverse event		disabil	itv	
death			\Box	nital anomaly	
life-threatening	(m adapyyr)		eniupen 🔲	d intervention t	o prevent
	· - initial or prolo			nent impairmen	t/damage
23 HOOPILEHZERION	- mittal or proto	ngea	other:		
3. Date of event 06/	28/1999		f. Date of this repor	1 09/02	/1000
(FE extension)			to explicit	03/02	/ 1999
5. Describe event or prob	Herri				-
Event (Na	ture of	Event	:)	Dx 4	Origin
	R FAILUR		-		orter
(Sx) ASCI				veb	
	DICE				
• • • • • • • • • • • • • • • • • • • •	PHALOPATI	HY			
	EASED PT				
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	ATED LIVE			1 00	
		IN EN			
	TDBEAR -				
(Sx) RESP	IRATORY D				
		ECOM	Pensati		
Narrative	: Initial	ECOMI	PENSATI	on his	
Narrative postmarke	: Initial	repo	PENSATI ort: T	ON his S was rea	
Narrative postmarket from a phy	: Initial ting case ysician a	reported in	ert: To the U	Con Chis S was red	ar old
Narrative postmarked from a phy male patie	: Initial ting case ysician a ent who r	reporting in a contract in a c	PENSATI ort: T the U volves ed Ara	Chis S was rec a 55 year	ar old
Narrative postmarked from a phy male patie unknown do	: Initial ting case ysician a ent who re ose for r	report from the front in the fr	PENSATION TO THE PERSON OF THE	chis S was rec a 55 yes va (leflu	ar old unomide)
Narrative postmarked from a phy male patie	: Initial ting case ysician a ent who re ose for r	report from the front in the fr	PENSATION TO THE PERSON OF THE	chis S was rec a 55 yes va (leflu	ar old unomide)
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Narrative postmarket from a phy male patie unknown do Specific t	: Initial ting case ysician a ant who r ose for r therapy d	report from the from	PENSATION TO THE PERSON OF THE	chis S was rec a 55 yes va (leflu	ar old unomide)
Narrative postmarket from a phy male patie unknown do Specific t	: Initial ting case ysician a ant who r ose for r therapy d	report from the from	PENSATION TO THE PERSON OF THE	chis S was rec a 55 yes va (leflu	ar old unomide)
Narrative postmarket from a phy male patie unknown do Specific t	: Initial ting case ysician a ant who r ose for r therapy d	report from the from	PENSATION TO THE PERSON OF THE	chis S was rec a 55 yes va (leflu	ar old unomide)
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Narrative postmarket from a phy male patie unknown do Specific t	: Initial ting case ysician a ant who r ose for r therapy d	report from the from	PENSATION TO THE PERSON OF THE	chis S was rec a 55 yes va (leflu	ar old unomide)
Narrative postmarket from a phy male patie unknown do Specific t	: Initial ting case ysician a ant who r ose for r therapy d	report from the from	PENSATION TO THE PERSON TO THE PERSON THE PE	chis S was rec a 55 yes va (leflu	ar old unomide)
Narrative postmarket from a phy male patie unknown do Specific t	: Initial ting case ysician a ant who r ose for r therapy d	report from the from	PENSATION TO THE PERSON TO THE PERSON THE PE	Chis S was rec a 55 yes va (leflu	ar old unomide)
Narrative postmarket from a phy male patie unknown do Specific t Relevant installaboratory	: Initial ting case vsician a ant who r ose for r cherapy di data including da	report from the from	PENSATI ort: T a the U volves ed Ara toid a are no	Chis S was rec a 55 yes va (leflu rthritis t known	ar old
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Narrative postmarket from a phy male patie unknown do Specific t Relevant instr/aboratory ther relevant history, inch noking and alcohol use.	: Initial ting case ysician a ant who r ose for r cherapy di data including da	report from nd in eceiv heuma ates	PENSATI ort: To the Unvolves ed Ara toid a are no	CON Chis S was rec a 55 year va (leflu rthritis t known s	ar old
Narrative postmarket from a phy male patie unknown do Specific t Relevant installaboratory	: Initial ting case ysician a ant who r ose for r cherapy di data including da	report from nd in eceiv heuma ates	PENSATI ort: To the Unvolves ed Ara toid a are no	CON Chis S was rec a 55 year va (leflu rthritis t known s	ar old
Narrative postmarket from a phy male patie unknown do Specific t Relevant insta/laboratory ther relevant history, inch moking and alcohol use.	: Initial ting case ysician a ant who r ose for r cherapy di data including da	report from the ceiv heumantes ites	ert: Tathe Unvolves ed Ara toid a are no	CON Chis S was recovered to the second sec	ar old unomide
Narrative postmarket from a phy male patie unknown do Specific t Relevant insta/laboratory ther relevant history, inch moking and alcohol use.	: Initial ting case ysician a ant who r ose for r cherapy di data including da	report from the ceiv heumantes ites	ert: Tathe Unvolves ed Ara toid a are no	CON Chis S was recovered to the second sec	ar old unomide
Narrative postmarket from a phy male patie unknown do Specific t Relevant installaboratory Wher relevant history, inclinious and alcohol use.	: Initial ting case ysician a ant who r ose for r cherapy di data including da	report from the ceiv he uma ates its	ert: The Unvolves ed Aratoid a are no conditions (ec.)	CIVEL	ar old unomide
Narrative postmarket from a phy male patie unknown do Specific t Relevant insta/laboratory ther relevant history, inch moking and alcohol use.	: Initial ting case ysician a ant who r ose for r cherapy di data including da	report from the ceiv he uma ates its	ert: The Unvolves ed Aratoid a are no conditions (ec.)	CON Chis S was recovered to the second sec	ar old unomide

admission that read cal personnet, user facility, distributor, manufacturer or product caused or contributed to the event.

item completed on continuation pages.

Domain Facsimile of EDA Enim 16002



echst Marion Roussel, Inc.

1	A.1. Patient Identifier	G.9. Mfr. report number	
MED WATCH		199920773HMRI	
			Page 2 of 2

B.5. Describe event or problem

[continuation:] however therapy was approximately 2 months duration. It is not indicated if the patient received a loading dose. Significant medical history includes alcohol dependency. Concomitant medications include allopurinol, co-trimoxazole, amitriptyline, lisinopril, fractionated heparin, prednisone, triamcinolone, and verapamil. The reporter states that on 28-Jun-99 the patient was hospitalized with increased PT, increased PTT, increased INR, ascites, jaundice, respiratory decompensation, elevated liver enzymes, encephalopathy, and liver failure. Leflunomide was discontinued on the date of admission to the hospital. The patient has received a total of 18 doses of cholestyramine, although it was not started until 2 weeks into the patient's hospitalization and therapy was not completed due to the extent of the patient's illness. The patient was intubated however, was extubated on 23-Aug-99. As of this report the patient's liver enzymes are still elevated (NOS). The reporter did not provide an assessment of causal relationship. No other information was received at the time of this report.

and the state of causal relationship. No other information was	received at the
Reporter assessment of the causal relationship between the adverse event as [_] Possible [_] Unlikely [_] Unrelated [_] Insufficient Data . If unlikely/unrelated, provide alternative explanation: [_] Illness [_] Concomitant Drug [_] Other	nd suspect drug:
C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)	
Unknown to 06/28/1999 Duration: 2 months	
C.10. Concomitant medical products and therapy dates (exclude treatment of event)	
[continuation:] HEPARIN-FRACTION, SODIUM SALT (LOVENOX) **UDNISONE** **ADNISONE** TRIANCINOLONE**	
VERAPANIL	

G.S. Adverse event term(s)

[continuation:] APNEA

E1. Name, address & phone

[continuation:] Oklahoma City, OK

UNITED STATES



MedWatch Forms (USA)

echst Marion Roussel, Inc.

	Approved by FDA on 3/22/94
Mfr report #	12 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
199813621HMRI	
UF/Dist report #	

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 2

THE TOTAL MEDICAL TROP		70104.41					FDA Use
 Patient inform 	nation			C. Suspect me	dication(s	5)	
	e at time event se	3. Sex	4. Weight	Name (give labeled streng	th & mfr/labeler.	if known)	
or -	event 55 yrs	Semale	lbs	#1 LEFLUNOMIDE	(ARAVA)	ablets	
in confidence of	birth: UNK	male	or kgs	#2 LEFLUNOMIDE	(ARAVA) I	ablets	
B. Adverse even	t or product pro	blem		2. Dose, frequency & route u	ısed	3. Therapy dat	es (if unknown, give duration)
1. Adverse event and		problem (e.g., defect	s/malfunctions)	#1 100 MG/DAY P	0	#1 #	All make)
2. Outcomes attributed to adv		problem (e.g., delect	S/IIdii uli (A/Olis)	20 1/2/22 20			
(check all that apply)		isability		4. Diagnosis for use (indicate		#2 *	
death 12/29/19	_ = = -	ongenital anomaly		#1 ARTHRITIS	on)		Event abated after use stoppe or dose reduced
life-threatening		equired intervention to ermanent impairment/o		, , , , , , , , , , , , , , , , , , , ,			#1 yes Ino doesn
hospitalization - initi	al or prolonged 🔀 o	ther: *		#2 ARTHRITIS			apply
3. Date of	4. Da			6. Lot#(if known)	7. Exp. d	ate (if known)	yes inot, doesn
event motory:	this	report 04/14/	1999	<u>#1</u>	_ #1		Event reappeared after reintroduction
Describe event or problem	(4.0			#2	#2		#1 yes no doesn
	,			9. NDC # · for product problem	ns anly (if known)	apply
Event (Natu:	re of Event)	Dx O	rigin	#1	#2		#2 yes no doesn'
(Dx) JAUNDIO	CE (FATAL OUT	COME) Repo	rter	10. Concomitant medical prod	lucts and therap	dates (exclude tr	eatment of event)
(Sx) BILIRU	BIN 22 (NOS)		1	LEVOTHYROXINE SOD			•
(Dx) ELEVATI	ED LIVER ENZYM	ŒS Repo	rter	HYDROXYCHLOROQUIN			NIL)
(FATAL	OUTCOME)			NAPROXEN (NAPROSY			
(Sx) AST 288	3			PROPRANOLOL HYDRO	CHLORIDE	(INDERAL)	*
(Sx) ALT 63				G. All manufactu	ırers		
• •	VE PHOSPHATASE	766		1. Contact office - name/addre		for devices)	2. Phone number
(UK) ILLIGHEL	'L THOUTHAIRDE	, , , , ,		Hoechst Marion Ro	ussel, Ind	c.	(816) 966-5000
N				10236 Marion Park	Drive		2 Donaton
	Initial report			Kansas City, MO			3. Report source (check all that apply)
- ,	ng case from t			64137			foreign
year old fer	male who was r	eceiving lef	Lunomide	•			study
-	ily for three	_	- 1				literature
	en 20 mg PO da						consumer
	chritis from 0		l l				∑ health
Nov-1998. S	Significant me	dical history	y is not	4. Date received by manufactur moteyr:		A# 20-905	professional
mentioned.	Concomitant m	edications in	nclude *	04/06/1999		O#	- Lace racing
. Relevant tests/laboratory data	a including dates	-00		6. W ND, protocol#			company representative
		กรอ	-	e. # PID, protocor#	PL	A#	distributor
					pre	9-1938 🔲 y	es other:
	0.0	R 2 0 1999		7. Type of report (check all that apply)	ОТ	C (-	
	АН	K 2 0 1555			pro	oduct 🗀 y	98
		P OHERS	ISTEM	5-day 🔀 15-day	8. Ach	erse event termis	;}
	ANVERSE	EVENT REPORTING SY	(0)	10-day periodic	JAUN	DICE, BILI	IRUBINEMIA, LIVER
	(April 1997)			☐ Initial ☐ follow-up #.			ABNORMAL, SGOT
				· · · · · · · · · · · · · · · · · · ·			PT INCREASED,
 Other relevant history, includ smoking and alcohol use, her 			ce, pregnancy.	9. Mr. report number	ALKA	Line Phose	PHATASE INCREASED
	, , , , , , , , , , , , , , , , , , , ,			199813621HMRI			
HISTORY OF A	LCOHOL ABUSE,	alcohol use		E. Initial reporter			
UNK				1. Name, address & phone #			
UNK	RI	TCETT!	الأرد	E.MICHAEL THELEN D	R		
UNK	Ì	NDD 1 0 1000		UNITED STATES 916-			
UNK +		APR 1 9 1999					
	ĺ						
Si	ulumission of a repor	t does not constan	le an				
	lmission that medica			2. Health professional?	3. Occupation		Initial reporter also sent report to FDA
	stributor, manufactu	•	sed or	∑ yes no		1	1 7 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
um sammakar CC	intributed to the eve	nt				i	yes no unk

contributed to the event.

Item completed on continuation pages.

Domain Facismée of ED& Econo 1500.4



rion Roussel, Inc.

	A.1. Patient identifier	G.9. Mfr. report number	
MED WATCH		199813621HMRI	
	<u> </u>		Page 2 of 2

B.2. Other outcome

medically important

8.5. Describe event or problem

[continuation:] Synthroid (levothyroxine sodium), Plaquenil (hydroxychloroquine phosphate), Naprosyn (naproxen), Inderal (propranolol hydrochloride), and Premarin (estrogens conjugated). The patient experienced jaundice and was evaluated by her physician and studies revealed: bilirubin 22, AST 288, ALT 63, and alkaline phosphatase 766. The hepatitis profile was negative. The event is ongoing at the time of this report. The physician feels the leflunomide was related to the jaundice and the elevated enzymes. The reporter's assessment of the causal relationship is that it cannot be excluded.

Addendum 06-Apr-1999: The physician returned the MedWatch form with this additional information: outcome attributed to adverse event: death 29-Dec-98; relevant medical history; history of alcohol abuse. No other additional information provided.

event t) JAUNDICE (FATAL OUTCOME) .x) BILIRUBIN 22 (NOS)	Serious YES	Dechal NO	Rechal NA		Alternative Explanation underlying/concomitant illness
	YES	мо	NA	Possible	underlying/concomitant illness

- (Sx) AST 288
- (Sx) ALT 63
- (Sx) ALKALINE PHOSPHATASE 766
- 8.7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] UNK

- C3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1) 11/09/1998 to 11/11/1998 Duration: 3 days
- C3. Therapy dates (if unknown, give duration) (morday/yr) (Suspect #2) 11/12/1998 to 11/13/1998 Duration: 2 days
- C.10. Concomitant medical products and therapy dates (exclude treatment of event)
 [continuation:] ESTROGENS CONJUGATED (PREMARIN)

DSS

APR 2 0 1999

ADVERSE EVENT REPORTING SYSTEM

RECEIVED
APR 1 9 1999
BY:_____

MedWatch Forms (USA)

Domain Facsimile	Approved by FOA on 3/22/94
Mfr report #	
200010080HMRI	
UF/Dist report #	
	FDA Use Only

Initial reporter also sent report to FDA

___yes

no 🗵 unk

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM	Page 1 of 2	
		FDA Use O
Patient information 1. Patient identifier 2. Age at time 3. Sex 4. Weight	C. Suspect medicati	
of event: 61 vrs	1. Name (give labeled strength & mfr/la	· · · · · · · · · · · · · · · · · · ·
or lbs	#1 LEFLUNOMIDE (ARAV.	A) Tablets
in confidence Of birth: UNK	METHOTREXATE Solu	tion NOS
B. Adverse event or product problem	2. Dose, frequency & route used	Therapy dates (if unknown, give duration) tends (or best eater ale)
1. Adverse event and/or Product problem (e.g., defects/malfunctions	#1 10 MG BID PO	#1
2. Outcomes attributed to adverse event	R	#2
(check all that apply)	4. Diagnosis for use (indication)	5. Event abated after use stopped
medical intervention to prevent	#1 RHEUMATOID ARTHRIT	IS or dose reduced
Life-threatening permanent impairment/damage		yes no doesn't
hospitalization - initial or prolonged other:	#2	apply yes no doesn't
3. Date of 4. Date of	7	apply
event 12/30/1999 this report 03/01/2000 (moltary);		8. Event reappeared after reintroduction
5. Describe event or problem	#2 #2	#1 yes no doesn't
Tuesda (Vintumo of Tuesda)	9. NDC#-for product problems only (if)	
Event (Nature of Event) Dx Origin	料	apply
(Dx) ELEVATED LIVER ENZYMES Reporter		herapy dates (exclude treatment of event)
(Dx) LETHARGY Reporter	ATENOLOL	
(Dx) CONFUSION Reporter	TRIAZOLAM (HALCION)	(VERAPAHIL - SLOW RELEASE)
(Dx) RESPIRATORY FAILURE Reporter	ALPRAZOLAM (XANAX)	(VERNIAMIL - SLOW RELEASE)
_	C. All manufacturers	
Narrative: Initial Report: this postmarketing	G. All manufacturers 1. Contact office - name/address (& mfn	ng site for devices) 2. Phone number
case, received by a pharmacist, involves a 61	Aventis Pharma, Inc.	(816) 966-5000
year old male who was receiving Arava	10236 Marion Park Drive	
(leflunomide) for treatment of rheumatoid	Kansas City, MO	3. Report source (check all that apply)
arthritis (doses and treatment dates not	64137	foreign
provided). Significant medical history	IMAI	R 0 3 2000 study
includes anxiety, benign prostatic	•	Literature
hyperplasia, cataract, hypertension,		consumer
rheumatoid arthritis and no known drug		health professional
allergies. Relevant concomitant medications	4. Date received by manufacturer (motolys)	5. (A)NDA # 20-905 user facility
were atenolol, Halcion (triazolam) *	02/25/2000	IND# company
6. Relevant tests/laboratory data, including dates	6. # ND, protocol #	PLA #
		distributor
,	7. Type of report	pre-1938yesother:
	(check all that apply)	OTC yes
Harry Company	☐ 5-day 🛛 15-day	product
MAR 0 6 ZOCO	10 40 40 10 10 10 10 10	3. Adverse event term(s)
$man \theta 6 2000$	1	LIVER FUNCTION TEST ABNORMAL,
1400	Initial S follow-up # 1	SOMNOLENCE, CONFUSION, APNEA
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy,	9. Mr. report number	
smoking and alcohol use, hepatic/renal dysfunction, etc.)	200010080HMRI	İ
CATARACT		
ANXIETY, BENIGNE PROSTATE HYPERPLASIA,	E. Initial reporter 1. Name, address & phone #	
HYPERTENSION, RHEUMATOID ARTHRITIS, NO KNOWN	JENNIFER BIU Ms.	ĺ
DRUG ALLERGIES	•	EDICAL CENTER, PHARMACY SERVICES
	30 PROSPECT AVE.	I SERVICES,
	HACKENSACK, NJ 07601 *	Ĭ
	1	

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.
Item completed on continuation pages

2.	Health professional?	3. Occupation
	⊠ yes ☐ no	
		İ



	A.1. Patient Identifier	G.9. Mfr. report number	
ED WATCH	TG	200010080HMRI	
			Page 2 of 2

B.5. Describe event or problem

[continuation:] methotrexate injections, verapamil hydrochloride and Xanax (alprazolam). On 30-Dec-1999 he presented to the emergency department with elevated liver enzymes, lethargy, confusion, and respiratory failure. The patient was placed on a ventilator and admitted to the Coronary Intensive Care Unit. Questran (cholestyramine) was started, following the recommended dosing for washout, on 01-Jan-2000. The outcome was listed as improving, no further information was available at the time of this report. Additional information will be provided upon receipt.

Laboratory data:	30-Dec am	30-Dec pm	04-Jan
TDH	16,376	3009	
AST	4600	2587	74
ALT		2215	422
tot. Bili		1.2	
dir. Bili		0.87	
Alk. Phos.	,	123	128

Addednum 25-Feb-2000: The reporting pharmacist returned the MedWatch with the following additional information: the dosing of leflunomide was 10 mg twice a day. The patient was in the Medical Intensive Care Unit and not the Coronary Intensive Care Unit. The cholestyramine was dosed at 8 grams every 8 hours for 11 days. AST was noted to be 4595 on 30-Dec-99 in the morning and not 4600 and the total bilirubin was 1.2 on 04-Jan-2000. No further additional information was received.

Reporter assessment of the causal relationship between the adverse event and suspect drug:
[_] Possible [_] Unlikely [_] Unrelated
[_] Insufficient Data
unlikely/unrelated, provide alternative explanation:
Illness [_] Concomitant Drug [_] Other

MAR 0 3 2000

E.1. Name, address & phone #

[continuation:] UNITED STATES 201-996-2583

MAR 0 6 2003

MedWatch Forms (USA)



MEDWATCH THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

.....armaceuticals, Inc.

Domain Facsimile	Approved by FDA on 3/22/5
Mir report #	
200123598US	
UF/Dist report #	
1	FCA Use Cres

				<u></u>		FCA
A. Patient information			C. Suspect med	dication/	-1	
Patient identifier 2. Age at time of event:	3. Sex	4. Weight	Name (give labeled streng	th & mfr/labeler	if known)	
0f65 yr	female	lbs				
in confidence Date of birth: 05/28/19	35 \boxtimes male	95 kg				
B. Adverse event or product p		<u>95</u> kgs				
1 `			2. Dose, frequency & route u	sed	3. Therapy day	ates (if ur known, give duration)
2. Outcomes attributed to adverse event	ict problem (e.g., defects	/malfunctions	1 20 MG QD PO		#1 *	
(check all that apply)	disability		#2		#2	•
death	congenital anomaly		4. Diagnosis for use (indicate	on)		5. Event abated after use st
(modayyri)	required intervention to p	revent	#1 RHEUMATOID AR	THRITIS		or dose reduced
hospitalization - initial or prolonged	permanent impairment/da	amage			÷ .	#1 yes no.', co
	other:		6. Lot # (if known)			ap
	Date of		#1 UNK	1	te (if known)	yes no do
(mo/day/yi)	this report 01/28/2	2002		#1		Event reappeared after reintroduction
5. Describe event or problem			#2	#2		#1 yes no doe
Event (Nature of Event)	D 0	استاست	9. NDC # - for product problems	only (if known)		app
(Dx) RENAL FAILURE		rigin	#1	#2		#2 yes no doe
(Sx) CREATININE (2.2-8.	Repor	rter	10. Concomitant medical produ	icts and therapy	dates (exclude t	treatment of events
(Dx) LIVER FAILURE	_		METHOTREXATE			or creating
(Dx) THROMBOCYTOPENIA	Repor	i	ROFECOXIB (VIOXX)			
(Dx) GANGRENOUS FINGERS	Repor	rter	PREDNISONE			
(14) GIZIGNENOUS FINGERS	AND TOES Repor	cter	CALCIUM *			
Narrative: Initial repor	an militar	j	G. All manufactur	rers		
Dostmarketing once	t: This sponta	neous	 Contact office - name/addres 	s (& mfring site i	or devices)	2. Phone number
postmarketing case, rece	lived from a		Aventis Pharmaceuti	cals, Inc	٠.	(908)243-6000
physician and an intensi	ve care nurse,		300 Somerset Corpor	ate Blvd.		
involves a 66 year old m	ale who initia	ted	Bridgewater, NJ			Report source (check all that apply)
therapy with Arava (lefl	unomide) 20mg	daily	08807-2854			foreign
in late Aug-2001 for the	umatoid arthri	tis.				study
No loading dose was give	n. The patien	t was				literature
admitted to the hospital	on 13-Dec-200	1 for	İ			consumer
renal and liver failure		į	I D			health
thrombocytopenia. The p	atient also	r	Date received by manufacturer (moreay/yr)		# 20-905	professional
developed gangrenous fin-	gers and toes a	and *	01/14/2002			user facility
Relevant tests/laboratory data, including dates			6 HIND protect !!	IND #		company representative
			6. If IND, protacol#	PLA #	·	d.stributor
				pre-19	938 <u> ye</u>	e i
			7. Type of report (check all that apply)	Отс	/-	other
			****	produ	ct <u> </u>	s
		į	☐ 5-day 🔀 15-day	8. Advers	e event term(s)	
			10-day periodic		FAILURE N	100 07-0-
			Initial \[\sum_ follow-up # 1	CREATI	NINE INCO	EASED, HEPATIC
Other relevant history including	44.4			FAILUR	E, THROMB	OCYTOPENIA.
Other relevant history, including preexisting medical comoking and alcohol use, hepatic/renal dysfunction, etc.)	nditions (e.g., allergies, race,	pregnancy.	9. Mfr. report number	GANGRE		
			200123598US			
VIRAL ILLNESS, SMOKER, ni	cotine use		E. Initial reporter			
RHEUMATOID ARTHRITIS		٠, ٦	E. Initial reporter 1. Name, address & phone #			
		ļ.	ANTHONY SEBBA MD			~
		2	36338 US HIGHWAY 19 N	ЮВТН		
!			PALM HARBOR, FL 34684			

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

2. Health professional?	3. Occupation	4. Initial reporter also	
yesne		sent report to FDA	
		= 1 \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	, unk ;

UNITED STATES 727-773-9793



maceuticals, Inc.

		G.9. Mfr. report number	
MED $f W$ ATCH	JP	200123598US	
			Page 2 of 2

B.5. Describe event or problem

[continuation:] will probably lose his fingertips. The patient began experiencing symptoms about 1 week prior to admission. Leflunomide and methotrexate were discontinued on the day of admission. The events were treated with Questran (cholestyramine) for 2 days, leucovorin, platelets, IV fluids and IVIG for 5 days. The events are resolving, and his labs are improving. His creatinine level decreased from 8.4 to 2.2. No other labs were known at the time of this report. Physician believed that these events could be due to the patient's consumption of oysters which possibly contained "vibro parahaemolyticus" or Salmonella. Concomitant medications include methotrexate, prednisone, Vioxx (rofecoxib), calcium and Centrum (multivitamin). Medical history is significant for a recent viral illness, rheumatoid arthritis, and he is a smoker.

Reporter's assessment of causal relationship: Possible.

Addendum for follow up received 14-Jan-2002: Nurse returned transcribed Medwatch form with note that it was reviewed and was OK. No additional infomation provided.

Addendum for follow-up received 17-Jan-2002: Patient's date of birth and weight provided.

Event (Dx) RENAL FAILURE (Sx) CREATININE (2.2-8.4)	Serious YES	Dechal NA	Rechal NA	Rpt.Causality Possible		Explanation or suspected cause
(Dx) LIVER FAILURE (Dx) THROMBOCYTOPENIA (Dx) GANGRENOUS FINGERS AND TOES	YES YES YES	NA NA NA	NA NA NA	Possible Possible Possible	other known	or suspected cause or suspected cause or suspected cause

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

08/??/2001 to 12/13/2001 Duration: 4 months

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] VITAMINS NOS, MINERALS NOS (CENTRUM)

MedWatch Forms (USA)



Ocmain Facsimile	AL From	4 by FDA 07 3229	
Mir report# 200022670US	,		
UF/Ois: report #			

i		EDA III. O	

5. Event abated after use stopped or dose reduced

8. Event reappeared after reintroduction

doesn't арріу doesn't

apply_

ccesn't

apply

ccesnit apply

MED WATCH		UF/Ost report #	
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM	Page 1 of 3		FDAUse
A. Patient information	C. Suspect	medication(s)	•
Patient identifier 2. Age at time of event: 3. Sex		trength & intrilabeler, if known;	

A Patient					C. Susp	ect medica	tion(s)	
Patient identifier	2. Age at bin of event	ne 66 yrs	3. Sex	4. Weight	1. Name (give a	beled strength & inf	rflabeler, if known)	
-21	10	00 718	female	lbs	#1 LEFLU	NOMIDE (ARA	VA) Tablets	
in confidence	Date : of birth:	04/05/1934	male	Or kos	#2	• •		
B. Adverse		product proble	200	kgs	2. Dose, frequen	 CV & route usad	3.75	
Adverse eve				-1-16			J. I nerapy (ga konto for basi ati #	i tes (di principio g I establic
2. Outcomes attributa		ent	olem (e.g., defect	s/mairunctions		•	#I	
roneck all that apply	′)	disabi	lity		#2		#2	
death Unix	nown	schge	nitai anomal,		4. Diagnosis for i			5. Event abate
we-inreater.			ed intervention to prent impairment of		#1 RHEUMA	TOID ARTHRI	TIS	; or dose red
hospitalizatio	on - initial or pr			anage	#2			₩1 yes
					6. Lot # (if known)	1 7.	Exp. date (if known)	#2 yes
	2/21/2000	4. Date of this repo	ort 01/17/	2001	#1 UNK	#1	•	8. Event reapp
Describe event or p		(Morday) (n)			112			reintroduction
COSCILOR SYSTEM OF P	rootom	,			9. NDC # - for pred	uct nichiems on w		#1 yes
Event (Nature o	f Event)	Dx O	rigin	#1	oct p colens on y ()		117
		TION TESTS		rter			-	yes yes
		W/ MASSIVE					i therapy dates (exclude t	realment of every;
	PATIC NE			i	IBUPROFEN (MOTRIN)		
(Dx) DIS	SSEMINAT	ED INTRAVASCI	JLAR Repo	rter	PREDNISONE	F (DDDIMATE)) 11/27/2000 to	
	AGULOPAT					d (FREVACID)	1 11/2//2000 €	Unknown
(Dx) COC	MBS TES	T POSITIVE N	OS Repo	rter	C All more	and the same		
	LLAPSED A		Rapo:	i	G. All mar			<u> </u>
		ITH BLEEDING	Repor	1	1		iring site for devices)	2. Phone
	TUS POST		Repor	1	Aventis Phar 10236 Marion			(816)
CAR	DIOPULM	NARY ARREST			Kansas City,		•	3. Repor
	ABOLIC A		Repor	rter	64137	-,		(check
		FAILURE	Repor	i	i ,			St.
		REATININE 3.	•		1			lite
	TIC	J.	Repor	tor				co
		KNOWN CAUSE	Repor					ne.
, ,			Kepoi	. CGI	4. Date received by m		5.	pro
Narrativ	e: Initi	al Report: T	his *	į	(170 day51) 01/10/2001	ļ	(A)NDA # 20-905	LSC
					31/10/2001	İ	IND#	cor
lelevant tests/laborat	ned catar lucifiqu	ng cares		!	6. If IND, protocol #		PLA#	rep
							pro 1039	dist
							pre-1938 ye	s i oth

cturers iddress (3 mfring site for devices) 2. Phone number Inc. (816) 966-5000 rk Drive 3. Report source (check all that apply) foreign stucy literature consumer nea th professiona 5. (A)NDA # _20-905 user facility IND# company representative PLA# distributor pre-1938 ... yes other 7. Type of report (check all that apply) OTC __ yes product __, 5-cay 🔯 15-day 8. Adverse event term(s) per odic LIVER FUNCTION TESTS NOS ABNORMAL, DISSEMINATED INTRAVASCULAR COAGULATION, COOMBS 9. Mfr. report number DIRECT TEST POSITIVE, COLLAPSE, 20002267008 DIARRHOMA HAMMORRHAGIC, +

Other relevant history, including pressisting modical conditions (e.g. allerges race pregnancy smoking and archicluse inepatiozenal dysfunction, etc.)

NO MENTION OF RELEVANT DISEASE



Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event tem completed on continuation pages

E. Initial reporter	
1. Name, address & phone #	500
James Wade, ND	DSS
CancerCareSpecialist	
2880 N Monroe St.	JAN 2 2 2001.

Health professional?	1. Occupation	4 Initial reportor also
yes no	Hematology	sent report to FDA yea an unix



A.1. Patient Identifier

MED WATCH

G.9. Mfr. report number

Page 2 cf 3

B.2. Other outcome

medically important

B.5. Describe event or problem

[continuation:] post-marketing case from the US was received from a lab tech and consulting hematologist. It involves a 66 year-old female who initiated therapy with Arava (leflunomide) 20 mg daily on 01-Dec-00 for rheumatoid arthritis. It is not reported whether the patient received a loading dose. Relevant medical history and concomitant medications were not reported. One week after initiating therapy with Arava, the patient experienced diarrhea. On 22-Dec-00, the patient collapsed at home and was admitted to the hospital. Liver function tests were consistent with massive hepatic necrosis, no values were reported. Lab tests showed disseminated intravascular coagulopathy and positive Coombs test. No values were provided. The patient was treated with charcoal and cholestyramine treatment was to begin today (25-Dec-00). She is currently on a ventilator in the intensive care unit. The primary care physician was contacted, no information was available.

Additional information was received on 27-Dec-00.

The patient's rheumatologist was not aware of her hospitalization. His office notes indicated that Arava 100mg weekly was initiated sometime at the end of November 2000. Laboratory work was to have been performed 2 weeks later but physicican had no laboratory reports. The patient was hospitalized approximately 3 weeks ago for abdominal pain (no other information available). Most recent admission was for cardiac and pulmonary arrest. The patient was resuscitated, intubated and is improving. The treating physicians at the hospital have not informed the rheumatologist or consulted with him.

The patient's primary care physician knew nothing about the patient's hospitalization other than she "had a reaction". Concomitant medications at last office visit on 27-Nov-2000 were ibuprofen, prednisone and lansoprazole.

Idendum for 08-Jan-01: Follow-up information was received from the hematologist and nurse at hospital. The physician provided the patient was status post cardiopulmonary arrest and on a ventilator. Dosage of Arava 20 mg daily since 01-Dec-00 was confirmed. Additional diagnoses provided were severe diarrhea with bleeding, metabolic acidosis, renal failure and receiving hemodialysis. Onset dates for these events were not provided. A nurse at the hospital indicated that the patient died. The date of death and cause of death were not known to her. She reported the patient had become septic, date not provided. Additional, follow-up information is being requested.

Addendum 10-Jan-2001: Follow-up received from the primary physician: The physician last saw the patient on 27-Nov-2000, where her only complaint was an upset stomach. She was prescribed lansoprazole. The leflunomide was started on 01-Dec-2000 by her rheumatologist. After two weeks ~14-Dec-2000, the patient reported to the rheumatologist that she was fine. The patient was admitted to the hospital on 21-Dec-2000 (not 22-Dec-2000 as previously reported) in full renal failure (creatinine 3.5), dehydrated and in cardiopulmonary arrest. The patient was placed on a ventilator. The patient 's liver enzymes were in the thousands, there was possible disseminated intravascular coagulation, the patient had terrible, strange smelling diarrhea, and the physician was unsure if the patient had episodes of parcxysmal atrial fibrillation. Family members gave conflicting reports on the course of events prior to hospitalization. One family member indicated that the patient had diarrhea for 2 weeks, another indicated 2 days. The patient did not report any diarrhea to her physicians. Her status was described as "everything fell spart at 2:00 PM the day before admission" to "she was fine all day". The physician could not understand the discreparcies. The consulting hematologist believed that the leflunomide caused the diarrhea and hepatic necrosis. Autopsy was performed which the results are not yet available with the aception that there was no evidence of coronary artery disease and the liver biopsy was reported to show only fatty liver. The patient had no prior history of renal failure.

Addendum for 11-Jan-01: Follow-up information was received from the rhaumatologist. He provided the patient had no history of alcohol use to his knowledge. Arava was initiated sometime in November, 2000. Liver enzymes on 28-Nov-00 were normal, AST/ALT were between 10-20, no units provided. The patient was treated in the past with methotrexate, "a long time ago". The only concomitant medication the physician was aware of was Motrin (ibuprofen). The rhaumatologist feels that there in insufficient evidence to make a causal assessment since "she could have come down with a virus". No other information is available to this physician.

JAN 2 2 200



A.1. Patient Identifier

MED WATCH

мω

G.9. Mfr. report number

20002267008

Page 3 of 3

8 5. Describe event or problem [continuation:]

CONS	t LIVER FUNCTION TESTS SISTENT W/ MASSIVE HEPATIC OSIS	Serious YES	Dechal	. Rechal NA	Rpt.Causality Possible	Alternative Explanation possibly associated with concomitant drug(s)
	DISSEMINATED INTRAVASCULAR ULOPATHY	YES	NA.	NA		underlying/concomitant illness
(Dx)	COOMBS TEST POSITIVE NOS	YES	NA	N/A		
(Dx)	COLLAPSED AT HOME	YES	UNK	UNK		,
(Dx)	DIARRHEA WITH BLEEDING	YES	UNK	UNK	Possible	possibly associated with
(Dx)	STATUS POST CARDIOPULMONARY	YES	NA	N.A		concomitant drug(s)
(Dx)	METABOLIC ACIDOSIS	YES	UNK	DNK		undanlar
(Dx)	ACUTE RENAL FAILURE	YES	NA	NA		underlying/componitant illness possibly associated with
(Sx)	INCREASED CREATININE 3.5					concomitant drug(s)
x)	SEPTIC	YES	UNK	UNX		possibly associated with
(Dx)	DEATH OF UNKNOWN CAUSE	YES	NA	n a		concomitant drug(s) underlying/concomitant illness

C3. Therapy dates (funknown gueduration) (mordaylyr) (Suspect#1) 11/??/2000 to 12/22/2000 Duration: 1 month

G.8. Adverse event term(s)

[continuation:] CARDIO-RESPIRATORY ARREST, METABOLIC ACIDOSIS NOS, RENAL FAILURE ACUTE, BLOOD CREATININE INCREASED, SEPSIS NOS, DEATH NOS

E.1. Name, address & phone

[continuation:] Decatur, IL 62526-3269

UNITED STATES 217-876-6600

DSS JAN 2 2 2001

MedWatch Forms (USA)

Individ	ual Safety	Report
		HILL II. II. III. III. III. III. III.

Aventis Pharmaceuticals, Inc.

Davis - 6		Approved by FDA on 3.1				
Oomain Facsinale Mfr report ♥						
200210502US						
L/F/Dist report #		***	-			
			FO4 Use Cat			

*3859484-X-00-01 *	Page 1 of 2		FDA Use Co
A. Patient information	C. Suspect medic	eation(e)	
1. Patient identifier 2. Age at time 3. Sex 4. Weight	Name (give labeled strength &		
JMV of event: 67 yrs femaleibs			
Or .			
of deat.			
B. Adverse event or product problem	2. Dose, frequency & route used	3. Therapy da دهد اه اهمانا	ites (if unknown, give duration) Leginally
Adverse event and/or Product problem (e.g., defects/malfunctions) #1 20 MG QD PO	#1 *	
Outcomes attributed to adverse event (check all that apply) disability	#2	#2	
death congenital anomaly	4. Diagnosis for use (indication)	· - · · - · · · · ·	5. Event abated after use stopped
(modayyr) required intervention to prevent	#1 RHEUMATOID ARTH	RITIS	or dose reduced
life-threatening permanent impairment/damage			#1 yes no doesn't
hospitalization - initial or prolonged defendance other:	#2 6. Lot # (f known)	<u></u>	#2yes! no doesn:
3. Date of 4. Date of	· ·	7. Exp. date (if known)	apply
event 10/??/2001 this report 01/22/2002 (modaylyr)	#1 UNK	- #1 i	8 Event reappeared after reintroduction
5. Describe event or problem	#2	#2	#1 yes no doesn)
Front (Nahara of Frank)	9. NDC # - for product problems or	ily (* known)	i – apo v
Event (Nature of Event) Dx Origin	#1	#2	yes no doesn't accy
(Dx) HEPATIC FAILURE Reporter (Sx) JAUNDICE	10. Concomitant medical products	and therapy dates (exclude	realment of eventy
1333, 3333, 232	UNKNOWN DRUG (UNKNOW	N DRUG)	
(Sx) TOTAL BILIRUBIN 25.1 (Sx) AST 61			
• • • • • • • • • • • • • • • • • • • •			
(8.)			
(Dx) DIARRHEA Reporter	G. All manufacture		
(Dx) WEAKNESS Reporter	Contact office - name/address (& mining site for devices)	2 Phone number
(Dx) PNEUMONIA Reporter	Aventis Pharmaceutic	•	(908)243-5000
(Sx) PULMONARY INFILTRATE	300 Somerset Corpora	te Blvd.	3. Report source
	Bridgewater, NJ 08807-2854		(check all that apply)
Narrative: Initial report 16-Jan-2002: This	00007-2034		foreign
postmarketing case reported by a physician			study
and pharmacists involves a 67-year-old	-		Jerature
female patient receiving Arava (leflunomide)	!		donsumer
20mg once a day for rheumatoid arthritis	4. Data recoved by manufacture	·	, health professiona
since September 2001. It is not indicated	4. Date received by manufacturer implications.	A)NDA # 20-905	user facility
if the patient received the loading dose *	01/16/2002	IND #	company
6. Relevant tests/laboratory data including dates	6. If IND, protocol #	PLA#	representative
, , , , , , , , , , , , , , , , , , ,		FERR	distributor
· · · · · · · · · · · · · · · · · · ·		cra-1938	ro F

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1111

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use thepatic/remail dysfunction, etc.)

HYPERTENSION, GASTRITIS, STEROID INDUCED DIABETES, SJOGREN'S SYNDROME, VERTEBRAL BASILAR INSUFFICIENCY, GERD, GRADE III ESOPHAGEAL VARICES PER EGD (12009 & 09/2001), ALLERGY TO ASPIRIN) ALLERGY TO FELDENE, ALLERGY TO MOTRIN, allergy

Sumain Facultina of analowin 1832 a

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event. Item completed on continuation pages

E. Initial reporter			
	_	 11.3	
	_	 	

7. Type of report

_ 10-day

miha:

9. Mfr. report number

200210502US

(check all that apply)

periodic

'allow-up #

1. Name, address & phone # GISELE BOURONCLE MD

153 CONCORD ST. ST. PAUL, MN 55107 UNITED STATES 651-602-7554

٠-					
2.	Health	profes	sional?	2.	Occupation.
	. 7	es	กบ		

отс

product

8. Adverse event term(s)

yes

HEPATIC FAILURE, JAUNDICE NOS,

BLOOD BILIRUBIN INCREASED.

ASPARTATE AMINCTRANSFERASE

INCREASED, BLOOD ALKALINE

PHOSPHATASE NOS INCREASED

4 Initial reporter also sant report to FDA .28



Aventis Pharmaceuticals, Inc.

MED WATCH	

A.1. Patient Identifier

JMV

G.9. Mfr. report number

200210502US

age 2 of 2

B.5. Describe event or problem

(continuation:) of leflunomide. Relevant medical history includes hypertension, gastritis, steroid induced diabetes, grade III esophageal varices (unknown etiology and unknown what further workup was performed) per EGD in 12/99 & 09/01, and allergies to aspirin, Feldene (piroxicam), and Motrin (ibuprofen). She has taken Imuran (azathioprine) and methotrexate in the past. She takes many concomitant medications (nos). Patient was seen by her primary care physician (reporter) on 16-Dec-2001 when she presented with yellow skin color. At this time, her total bilirubin was 9.5, AST 48, ALT 27, and alkaline phosphatase 160. She was diagnosed with jaundice. Arava was discontinued on -25-Dec-2001. On 03-Jan-2002, the patient presented to the hospital with pulmonary infiltrates and jaundice. Her total bilirubin was increased to 19 at this time. She was treated for pneumonia and had further workup for liver disease (multiple labs) and liver biopsy. She was discharged on 11-Jan-2002. On 14-Jan-2002, she presented to a different hospital with diarrhea, weakness, and jaundice. Liver biopsy results (January 2002) showed "fibrosis and marked canalicular cholestasis suggestive of possible medication reaction". She was started on Questran (cholestyramine) '8 gram by mouth every 8 hours to "increase in the elimination of Arava" (January 2001 Her abdominal CT from December 2001 shows "hepatic cirrhosis with varices". The events are engoing. Arava was prescribed by the patient's rheumatologist. She is currently being worked up for a liver transplant. Onset date of the above event: -October 2001.

Her labs are as follows:

14-Jan-2002: INR--1.5, NH3--47, total bilirubin--25.1, AST--61, ALT--31, alkaline phosphatase--151
15-Jan-2002: INR--1.5, NH3--75, total bilirubin--21.2, AST--59, ALT--29, alkaline phosphatase--145
16-Jan-2002: INR--1.5, NH3--83, total bilirubin--20.7, AST--59, ALT--28, alkaline phosphatase--132
No additional information was provided.

The reporter's causal assessment between Arava and the events are unknown.

Reporter assessment of the causal relationship between	the	adverse	event	and	suspect	drug:
[_] Possible [_] Unlikely [_] Unrelated						
[_] Insufficient Data						
If unlikely/unrelated, provide alternative explanation:						
[] Illness [] Concomitant Drug [] Other						

C.3. Therapy dates (if unknown give duration) (mo/day.yr) (Suspect #1) 09/??/2001 to 12/25/2001 Duration: 3 months

G.8. Adverse event term(s)

(continuation:) DIARRHOEA NOS, WEAKNESS, PNEUMONIA NOS, LUNG INFILTRATION NOS

DSS

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For VOLUNTARY reporting
CD by health professionals of adverse
Evenus and product problems

		-	control of the same
POR Use Only (
	16	120	79
	f_B_,		

THE FOR MEDICAL PRODUCTS REPORTING PROGRAM	_ d (\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \
A. Patient information	C. Suspect medication(s)
1. Politing lawrellur 2. Age at time at amount 17 3. Sex 4. Weight 17 17 1 1 1 1 10 10 10 10 10 10 10 10 10 10 1	Name (give labeled strength & mitr/speler, if known)
	The state of the s
in confidence of birth: 9/2/34 male 590/kg	2. Dose, frequency & route used 3. Therapy dates (if unknown, pive duration
B. Adverse event or product problem	as 20 - 12/
Affiveres event entitor Product problem (e.g., detects/me(functions) Our comes attributed to adverse event	aumy po go "applex 4/61 - 17/6
(check of that apply) (check of that apply) (congenital anomaly	4. Diagnosis for use (indication) , 5. Event absted after use
required intervention to prevent	10 Pheumohid Arthuits Mapped or dose reduce
hospitalization – initial or prolonged oshor:	#1 yes 2 no does
1. Date of Anguera 14. Date of 1/1	d. Lat a (if known) 7. Exp. dete (if known) 82 yes no does app)
	81 8. Event reappeared after reintroduction
5. Describe syst or problem	92 PV S Affect and an application of the second of the sec
12/99 EGO showed Grode III Esophogue	
varices - unknown etidogy = unknown	10. Concomitant medical products and therapy dates (outlide treatment of event)
what further workup was performed.	
Hrave started approx 9/01. Presented	
to kaspital 1/3/02 E pulm infitrats	l l
1 10144 drag 4 T. 615 119 \ 7120759 19	D. Suspect medical device
precuminea - hustrer worker of liver	1. Brand name
descare lower ale laber + little billetin	2. Type of device
Discharged 1/1/12 Presented to all	3. Manufacturar Agric & address 4. Operator of device
hairtal lives - diarrige Wildkings -	praith professional
intradice him home tellets opported	DENCINED Sky user/paliers
	RECEIVED /
stacked to mereous elemination	5. Expiration date
12/01 MA Abdoneu CI: Repoticorrehasis & Varieto	6.
6. Relevant tests/aberatory data, including dates	MEDWATCHCTU 7. 19 Implanted, give date
1/14/02: INR-1.5 1/15/02: INR-1.5 1/16/02: INR=1.5	HIP O 4 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
NH3 - 47 NH3 - 75 NH3 - 83 Tbili = 25 1 Tbili = 212 Tbili - 207	acrial 9
Tbili = 25.1 T.bili = 212 Tbili = 20.7 AST - 61 AST - 59 AST - 59	
1 2 21	9. Device evallable for gratuation? (Do not send to FDA)
AIRPAN -13. AIRPAS-173 AIRPAS-132	Yes no returned to manufacturer on
You Liver biopsy : Fibresia , marked Canalicular Chalestosis	10. Concernitant gladical products and therapy dates (exclude insalment of event)
7. Other relations, Industrial prescriptions (e.g., alorges,	
rece, pregnancy, emoking and alcohol use, hepatic/renal dysfunction, etc.) HTM	
Remarbid Arthrits	E. Reporter (see contidentiality section on back) 1. Name, address & shore #
Sjogrens Syndrame	CARRIE WEINER Pharms
GERO A allega to lab le rance	333 N & mith AVL
Skroid induced glucal interance. Verkoral basilar insufficiency	St Paul MU 55102
Previous ux a Imuran + MTX (? dates)	2. Meetip provisational? 3. Occupation , 4. Also reported to
Mail to: MEDWATCH OF FAX to:	1 you 1 no Pharmacest 1 manufacturer
\$600 Fighers Lane 1-800-FDA-0178 Rockville, MO 20852-9787	Wyou do NOT went your identity disclosed in
	the menufacturer, place an "X" in this bag.
MENYATOLD	USS.
A A MALINE MANAGEMENT OF THE STATE OF THE ST	

CTV161239 MEDWATCH

ARPS DRUG INFORMATION® 2001

FEB 1 0 2002

FEB 0 8 2002

MedWatch Forms (USA)

individual Safety Report

)LUNTARY reporting h professionals of adverse s and product problems

		See OME SMARKERS OF THEFTH
fba Um: Only		
Tylinger code andstancia F	14	3047

THE PUR MEDI HE PRODUCTS REPORTING PROGRAM

INE PUA MEDI	T PRODUCTS ASPORTING PROCESS		
A. Patien	htermation	C. Suspect medication(s)	
1. Patient identif	2. Age it time 1. Sax 4. Weight	1. Name (Product Name) (Labeled 3เกษายุปก)	(Mfr/Labeler)
ne.	or	" Armodassal	<u> </u>
ベン	Date	n/estunnill	/
in confidence	of birth: kgs.	2. Doed requency/Route used 3. Therapy date	To for best estimate)
B. Advers	event or product problem At and/or Product problem (e.g., defects/malfunctions)	#1 / #1 ********************************	
1. Adverse	ent and/or Product problem (e.g., defects/mailunctions)	W2 / / W2	-
2. Outcomes att (check all that	(I/V) disability		5. Event abated after use
death _	congenital anomaly	#1	stopped or dose reduced
ide-threak	required intervention to pravent pomenant impairmenVdamage	T1	#1 yes no doesn't
husphaltzi	in - Initial or prolonged Other.	#2	#2 yes no doesn'
	/ I4. Date of	6. Lot # (If known) 7. Exp. date (if known)	
3. Date of avent /	1/12/1999 this report 4/24/2000	#1	 Event respected after reintroduction
5 Describe eve	cr problem	#2 #2	#1 yes no doesn'
-1	and have the	9, NDC # (for product problems only)	
Pt ud	rithed 20 MLATS, MS DO		12 yes no doesn't
/	ne a serie do uno x	10. Concomitant medical products and therapy states (ex	clude treatment of event)
108807	7 2' amiodaione 4		
/.	Medo distantinues		
afeur	mide.		
la all	mide Meds dissontinued int A less confused intproved	D Suspect medical device	
onau	nuc 11. 22 ding	1 Brand name	
V M	1 mmille		
FFIG	11,11.20	2. Type of device	•
		3. Manufacturer name & eddress	4. Operator of device
			health professional
	!		lay user/patient
)		U other
	į	RECEIVED	
	j		5. Expiration date
		8. model # MAY 1 0 7081	(100-02)
		model #ittet i // (//// i	7. If Implented, give date
6. Relevant tasti	3borstory date, including dates	catalog #	(mindahmyd)
<i>C</i> 1		perial 9 IVICUVVATORIOTO	
	L - foren -	lot#	8. If explanted, give date
	+ - Follow - c.		
		9, Device available for evaluation? (Do not send	lo FDA\
	1	yea no returned to menufactur	ter on
	j	10. Concomitant medical products and therapy clates (exc	lude treatment of event)
7 Other relevan	story, including preexisting medical conditions		
(e.g., zijerojes, rac	pregnancy, emoking and alcohol use, hapetic/renul dystunction, etc.)		
Want	· C 20 transpusion	E. Reporter (see confidentiality section	
P. Spanie	an MA Alph Nell	Jamie Pack, Phanes 312-9	12-4525
HM,	CA, OA, AGB, OH	Jamie Mek, Phanes ony Inforgation Service, each	Medical ON
, ,		una ul con exist Parkety	
		1633 W. Con griss Parkning	
1	143647	2. Health professional? 3. Occupation	4. Also reported to
		X res - Marmaust	manufacturer
A	Mail to: MEDWATCH or FAX to:	5. If you do not want your identity disclosed to	user facility
	5600 Finhers Lane 1-800-FDA-4176 Rockville, MD 20652-9787	the manufacturer, piece en "X" in this box.	distributor
4.4	_	At a modern personal architectural property	within had to the event

MedWatch Forms (USA)



The FDA Safety Information and Adverse Event Reporting Program

VOLUNTARY reporting of adverse events and product problems

CDEFi

FDA Use Only

A. Patient	information				C. Suspect			d to R.Bundlia
1. Patient identifier JH		Years	3. Sex 4. V	Velght —— Ibs	1. Name (give label Leflunomide	ed strength & mir/	labeler, if known	Aventis
In confidence	Date of birth:		male	ot			North House Control of the Control o	
				kgs	#2			
1. Adverse eve	event or prod				2. Dose, frequency 20 mg day		3. Therapy in the form to lor be	dates (if unknown, give duration
	ent and/or	roduct problem	(e.g., defects/malfun	ictions)	#1 25 mg day	Oral	*1 04/01/	1999 09/09/1999
(check all that ap	uwa to saverse event ply)	disability			#2		*2	
death 09	/12/1999	ongenita	l anomaly		4. Diagnosis for use	(indication)	1 **2	Ts ====================================
life-threatenin	(mo/dey/ys)	required i	ntervention to prever	nt I	#1 rheumatoid			 Event abated after use stopped or dose reduce
1 =	-	permaner	impairment/damag	e				1 _
nospitalization	n - initial or prolonged	other:		- 1	#2			#1 yes no does
3. Date of		4. Date of		-	6. Lot # (if known)	7. Ехр.	date (if known)	doesr
event 09/05 (mordayryr)	9/1999	this report	03/26/2002		#1	#1		8. Event reappeared after
5. Describe event o					#2	#2		reintroduction
75 y/o fema	le with a 5	year histo	ory of	- 1	Q NDC # (for over day)	. [#1 yes no doesr
rneumatoid	arthritis and	d cutaneou	is lunu	İ	9. NDC # (for product	problems only)		
was started	on leflurom	ide in Apr	ril of	- 1	10 Concomitant	digal product		#2 yes no doesn
including T.	had laborato FTs which wer	res every	/ 6 weeks	1	Accupril 10	micar proceucts an	u inerapy dates i	exclude treatment of event)
hadaknown	history of a	itrial			Prilosec 10	mg OD Pr	conafenon	g QD e 225 mg TID
fibrillation	n for which s	he was tr	reated	- 1	Premarin U	.625 mg OI	Plaque	nil 200 ma
with Propafo	enone and cou	madin. ()n		QD Amio	_	•	Boc mg
irregular b	e was admitte	d for a f	ast		D. Cuencet			
150 but was	eart beat. H hemodynamica	er neart	rate was		D. Suspect n	nedical dev	ice	
9/10/1999 st	ne was conver	ted with	e. on	i i	i. Diang name			
electrical o	cardioversion	and give	n one	- 11	2. Type of device		······································	
doe of Amio	darone. Late	r that mo	rning on					
9/10, her la	boratories r	eturned a	nd AST =		3. Manufacturer name	& address		4. Operator of device
58 Over th	T = 669 and ne next 2 day	her Alk P	hos =	11				health professional
progressive	liver failur	s she wen e and nac	t into	11				lay user/patient
on 9/12/1999	With the AS	T = 4682	the ALT		DE	<u> </u>		other:
= 2202, the	Tot Bili = 3	and the	Alk Phos		コロ	CEIVE	-1)	
= 92. The 1	eflunomide a	nd amioda:	rone -1					5. Expiration date
had been	ere stopped	and the p	atient	1 1	MAI	R 3 0 2002	,	(moday/yr)
	pratory data, including	dates		[
The creatnin	e was normal?	ly 0.8, bi	it on		etalog MEDW	ATCH C	TH	7. If implanted, give date
admission, i	t was 1.9 and	d on the d	dav of		erial #	1110110	110	(mordey/yr)
her death it	was 2.6. Or	n admissio	on, the					
the albumin	he HCO3 = 20, = 2.5 and the	the BUN	= 53,	1 10	ot#			8. If explanted, give date (mc/day/yi)
-normally 1.	= 2.5 and the 6 to 2.0=	: 1NK = 5.	. /		ther #			Dee
				9	Device available for	evaluation?	(Do not send	IN EDA)
					yes n	o retur	ned to manufactu	rer on
				10). Concomitant medic	al products and it	herany dates /ox	dude treatment of event
						and the	iciapy dates (ex	aude treatment of eventy
race, preglancy, sm	ory, including preexist loking and alcohol use.	ing medical con	ditions (e.g., allergie	25.				
There was no	history of a	lcohol in	take					
nepatitis or	exposure to	other liv	er		. Reporter (se	e confidentia	lity section	on back)
toxins.		11	7	- 1.	Name & address	phor	520-62	6-6399
	Λ.	(EUIX	ATCH	D.	avid E. Yocum, N	(D		
	1.0	TUUV	HILLI	R	pom 8303, 1501 N	Campbell A	ve	
٤		4413.0			JCSON	N	izona	255
CIG	44596	MAR 2	7 2002	, ,	nited States		izona 1. arizona . ec	85724 Bu
000	47776				Health professional?	3. Occupation		Also reported to
Mail	to: MEDWAPE	- AL	FAXAONIS IIIS		yes no	Physician	1	manufacturer
	5600 Flahe		HO DA 51 18	5	If you do NOT want y	our identity dis-1	or od to	user facility
	nockville, mu		, v L		the manufacturer, pla	ce an " X " in this	s box.	distributor

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.



164596

MED**V**ATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems

Internet Submission - Page 2 c 3

B5. Describe event or problem continued

put on cholestyramine 4 grams TID without effect. Her family refuse an autopsy.

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MAR 3 0 2007

MEDWATCH CTU

DSS

MAR 3 U 2002

Mail to: MEDWATCH

5600 Fishers Lane Rockville, MD 20852-9787

or FAX to: 1-800-FDA-0178

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For VOLUNTARY reporting by health professionals of adverse events and product problems Internet Submission - Page 5 3 5 2 3

C10. Concomitant medical products and therapy dates continued

darone 800mg -one dose-

D10. Concomitant medical products and therapy dates continued

RECEIVED

MAR 3 0 2002

MEDWATCH CTL

MAR 3 U 2002

Mail to: MEDWATCH

5600 Fishers Lane Rockville, MD 20852-9787

104596

or FAX to:

1-800-FDA-0178

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MedWatch Forms (USA)



by health professionals of adverse events and product problems

Internet Stanff Rion - Page 1 66 2

FDA Use Only	See OMB statement on reversi
Triage unit sequence #	128229
Ches	

THE TON MEDICAL PRODUCTS ACTIVITING PROGRAM	
A. Patient information	C. Suspect medication(s)
1. Patient identifier 2. Age at time Sex Weight	Name (Product Name) (Laboled Strongth)
CI of evint: 12 Yours I female b	Acava / 20mg / Hoechst Marion
In confidence of birth: 08/08/1923 male kg	#2 Acetaminopher. / 100kg / Unknown
B. Adverse event or product problem	2 DoseiFrequency/Route used 3. Therapy dates iff unknown, give duration
1. Adverse event and/or Product problem (e.g., defects/malfunctions)	From To for best estimate #1 07/12/1999 = 07/12/2000
Outcomes attributed to adverse event (check all that apply) disability	$\#2\frac{-975m}{g}$ / $\frac{4}{t0.6}$ / Oral $\#202/C1/2000 - 07/12/2000$
death congenital anomaly	4 Diagnosis for use (separate indications with commus) 5 Event abated after use
required intervention prevent required intervention requiremain pairing requiremain	#1 Rheumatoid Arthritis stopped or cose reduce
hospitalization – initia or prolonged other:	#2 Pain #1 yes no cees
3 Date of 4 Date of	6. Lot # (if known) 7. Exp. date (if known) #2 Vyes no does apply
event 07/11/2000 this report 08/30/2000 (moddlyry)	#1 #1 8. Event reappeared after
5 Describe event or problem	#2 #2 reintroduction
76yof with rheumatoid arthritis receiving	9. NDC # (for product problems un y) #1 yes no vidoes apply
prednisone, Arava, Pércocet -one tab q4h prn-, and Tylenol -650 mg qid prn-	#2 ☐ yes ☐ no ☑ does
-duration of use of	10 Concomitant medical products and therapy dates (exclude treatment of event)
acetaminophen-containing products is	MEDICATIONS ON TRANSFER: Duragesic patch,
unclear- was admitted from outside	50 mg every 72 hours; Calcium carbonate
hospital on 7/11/00 after increasing	500 mg p.o. q. day; Magnesium oxide 400
confusion, BP of 80/50, positive	mg
hemocult, ammonia level of 85, AST of >	D. Suspect medical device
4500, ALT of 1019, bilirubin of 1.2, alk phos of 195, PT greater than 33, albumin	1. Brand name
of 2.8, and with a pulse-ox reading of	,
96%. Patient had no prior history of	2. Type of device
alcohol use or liver disease. Patient was	3. Manufacturer name & address DSS 4. Operator of device
provided supportive therapy and treated	
with N-aceytlcysteine and Vitamin K. AST	AUG 3 1 2000 health professional
improved to 62, ALT to 78, alkaline phoshatase to 102 by 7/16. Bilirubin	tay use */patient
peaked at 2.4 and decreased to 1.0 by	other
7/26/00.	
	5 Expiration date
	© RECEIVED on de tayyo
6. Relevant tests/laboratory data, including dates	
BP cf 80/50, positive hemocult, ammonia	catalog #AUG 3 1 2000; 7 If implanted, give date
level of 85, AST of > 4500. ALT of 1019,	
bilirubin of 1.2, alk phos of 195, PT	lot # MEDWATCH CTL 8 If explanted, give date
greater than 33, albumin of 2.8, and with a pulse-ox reading of 96%. After	THE DIAM TO THE CONTROL OF THE CONTR
treatment and discontination of suspect	other #
drugs AST improved to 62, ALT to 78,	9. Device available for evaluation? (Do not send device to FDA)
alkaline phoshatase to 102 by 7/18	yes no returned to manufacturer or.
Bilirubin peaked at 2.4 and decreased to	10 Concomitant medical products and therapy cales (exclude treatment of event)
1.0 by 7/26/00.	
 Other relevant history, including preexisting medical conditions (e.g., allergies irace pregnancy, smoking and alcoholiuse, hepatic/renal dysfunction, etc.) 	
Past medical history of rheumatoid	E. Donorton (
arthritis, history of osteoarthritis	E. Reporter (see confidentiality section on back)
involving the lumbar spine, status	412 524-4987
postdecompression and fusion of the lumbar spine, history of COPD, history of	Peg Verrico, RPn University of Pittsburgh Medical Center 1-7 /.mtur.a
systemic hypertension, status post right	Hall
tibial fracture. Past surgical history	Pittsburgh Pennsylvania 15261
arthroplasties of both knees and CRIF	United States /erricommamsk.upmc.edu. 2 Health professional? 3 Occupation 4 Also reported to
Mail to: MEDWATCH 1-4FAX to:	
5500 Francis Line Rocky 12 December 570	5 If you do not want your identity disclosed to the manufacturer, place an "X" in this box.
Rockvick D. Deduct St. T. T. C.D.	(30.6.7)

CTW 128229



MEDWATCH

For VOLUNTARY reporting by health professionals of adverse events and product problems
Internet Submission - Page & 2 4 4

C10. Concomitant medical products and therapy dates continued

p.o. q.day; Prednische 5 mg p.o. q. day; Paxil 40 mg p.o. q. day; Prinivil 5 mg p.o. q. day; Zantac 150 mg p.o. q. day; Colace 1 p.o. b.i.d.

f/ recover

D10. Concomitant medical products and therapy dates continued

DSS AUG 3 1 2000

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

Submission of a report does not constitute an admission that medical became or the product caused or contributed to the event.

MedWatch Forms (USA)



3. Sex

Aventis Pharma, Inc.

Domain Factor in	Accrave	15 50.	
Mir report #	- SPD GAR	1 by FDA 20 3/22	794
200010951HMRI			
UF-Dist report #			

THE FDA MEDIC	AL PRODUCTS REPO	RTING PROCEAL
	WELL CODOCIONEL	MINU PROUKAN

2. Age at time

Patient information

4. Weight

ie reduced	r use stopped
abated after	r use stopped
abated after	r use stopped
ie reduced	
ie reduced	
res no	doeshit appiy
es no	dbesnit appiy
reappeared duction	
es no	doesn t apply
	doesnit apply
•	

??	or ———	K	female	1	bs
in confidence	Date UNK of birth:		male	or k	gs
B. Adverse	event or produc	t probler	n		Ė
1. 🖄 Adverse ever	nt and/or		em (e.g., defects	s/malfunctio	ons
Outcomes attributed (check all that apply)	to adverse event				_
	1/2000	disabilit	y ital anomaly		
life-threatenin	(mo/dayiye)	required	intervention to j	prevent	
	n - initial or prolonged	perman other:	ent impairment/d	amage	
		7		· M	
(maldayiyr)	/??/2000	4. Date of this report	03/27/2	000	
5. Describe event or pro	blem ,				Ī
Event (N	ature of Even	t)	Dx Or	iain	İ
(Dx) NEA	R SYNCOPAL EP	ISODE	Repor	-	
(Dx) SHO	CK (FATAL)		Repor		
(Dx) LIV	ER FAILURE		Report	ter	
(Dx) PAN	CREATITIS		Report	ter	
(Dx) INT	ERSTITIAL LUN	G DISEAS	E Report	ter	
(FA	TAL)				
Mammakini					
Narrative			his		
	eting case fro ysician and i			eived	l
	of unknown age			~	
	de (Arava) 10				İ
3 day loa	ding dose the	n 20 ma	orally da	ilv	
	atoid arthrit				
Mar-2000.					
includes	interstitial			*	
Relevant tests/laborator					1
					!
					:
					!
Other relevant history, if smoking and alcohol use	nepatic/renail dysfunction	cal conditions (on letc.)	e g., allergies, race	pregnancy	

G. All manufacturers 1. Contact office - name/address (& mfring site for devices) 2. Phone number Aventis Pharma, Inc. (816) 966-5000 10236 Marion Park Drive 3. Report source Kansas City, MO (check all that apply) 64137 foreign study __ literature MAR 29 2000 consumer nealth 4. Date received by manufacturer professional (A)NDA # 20-905 user facility 03/16/2000 IND# representative 6. If IND, protocol # PLA# distributor pre-1938 other 7 Type of report (check all that apply) OTC . yes product 5-day 15-day 8. Adverse event term(s) 10-day . _ periodic DIZZINESS, SHOCK, LIVER FAILURE PANCREATITIS, INTERSTITIAL , follow-up # PNEUMONIA 9. Mfr. report number 200010951HMRI

INTERSTITIAL LUNG DISEASE

MAR 3 0 2000



7.

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event. Item completed on continuation pages

<u>E. li</u>	nii	ial	re	рo	rte	1
--------------	-----	-----	----	----	-----	---

1 Name, address & phone #

MITCHELL FEINMAN MD 1737 VILLAGE PARK DRIVE ORANGEBURG, SC 29118 UNITED STATES 803-539-2224

2	Health professional?	3. Occupation	4 Initial reporter assignment	
	yes no		sent report to FDA	
			yes no c	in k
_				



n. I. Patient Identifier

Aventis Pharma, Inc.

MED WATCH

22

G.9. Mfr. report number

200010951HMRI

Page 2 of 2

B.5. Describe event or problem

[continuation] relevant consemitant medicative Associationed. In Mar-2000, the patient presented to the emergency room with a near syncopal episode and shock NOS. The patient was hospitalized with liver failure, pancreatitis, and interstitial lung disease, and subsequently died on 01-Mar-2000. Arava was discontinued upon hospitalization, but the patient did not undergo a washout.

Additional information has been requested and will be forwarded upon receipt.

Reporter's assessment of causal relationship: Cannot be excluded.

Event	Serious	Dechal	Rechal	Rpt.Causality	816
(Dx) NEAR SYNCOPAL EPISODE	YES	UNK	NA	Possible	Alternative Explanation
(Dx) SHOCK (FATAL)	YES	UNK	NA	Possible	
(Dx) LIVER FAILURE	YES	UNK	NA.	Possible	
(Dx) PANCREATITIS	YES	UNK	NA.	Possible	
(Dx) INTERSTITIAL LUNG DISEASE	YES	UNK	NA	Possible	
(FATAL)		••••	.121	tossible	

C.3. Therapy dates (if unknown give duration) (mo/day/yr) (Suspect #1) 12/??/1999 to 12/??/1999 Duration: 3 days

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #2) 12/??/1999 to 03/??/2000 Duration: 3 months

MAR 2 9 2000

DSS MAR 3 0 2000

MedWatch Forms (USA)

Domain Factimize of



Hoechst Marion Roussel, Inc.

Domain Facsimile	Approved by FDA on 3/22/94
ifrreport # 199922130HMRI	
DF/Dist report #	
	FDA Ura Onlin

*34248	01-1-00-01+				Page 1 of 2			FDA Use O
Patient in	formation				C. Suspect med			
	2. Age at time		3. Sex	4. Weight	1. Name (give labeled strength			
	of event:	NK	female	lbs	#1 LEFLUNOMIDE	(ARAVA) T	ablets	
64	Date		male	or kgs	#2			
in confidence	of birth:	est proble	l		2. Dose, frequency & route us	sed	3. Therapy date	s (if unknown, give curation)
arriva.	event or produ		olem (e.g., defec	ts/malfunctions)	#1		#1	
Adverse even Outcomes attributed		- ,	(0.3.,		#2		#2	
(check all that apply)		disabi	lity mital anomaly		4. Diagnosis for use (indication	(רכ		Event abated after use stopp or dose reduced
death	gm o/dary/yr)		ed intervention to	prevent	#1 UNKNOWN			#1 yes no doesn
🔀 life-threatenin	ıg		nent impairment		#2			apply
hospitalization	n - initial or prolonge	d other:			6. Lot#(if known)	7. Exp. d	late (if known)	#2 t jyes ! not_ doesn apply
Date of		4. Date of	ort 12/15	/1999	#1 UNK	#1		Event reappeared after reintroduction
event madayyi)		this repo	ort 12/13	/1333	#2	#2		#1 yes no doesn
Describe event or pro	oblem	•			9. NDC # - for product problem	's chiy (if know)	n)	apply
Fuent ()	Nature of Ev	rent)	D x	Origin	#1	#2		#2 yes no doesn
	PATIC FAILUR			orter	10. Concornitant medical prod	lucts and therap	y dates (exclude tr	
(Sx) JAU			•	j	UNKNOWN DRUG (UNK			
• •	EVATED BILIF	RUBIN NOS						
	EVATED ALKAI							
	SPHATASE							
(Dx) VA	SCULITIS		Rep	orter	G. All manufactu 1. Contact office - name/addn		to for deveces	2. Phone number
,,,,					Hoechst Marion Ro			(816) 966-5000
Narrati	ve: This US	spontane	ous postm	arketing	10236 Marion Park			3. Report source
	ported by a				Kansas City, MO			(check all that acpiv)
	(age and ge				64137			foreign
	ng ARAVA (le					DE	C 2 0	study
indicat	ion, and the	erapy dat	es were n	ot				literature
provide	d. On an w	nspecifie	ed date, t	he				consumer health
patient	experience	d an elev	ated bili	rubin	4. Date received by manufactu	rer 5.		professional
	undice, ele				uno/day/yri	(A)	NDA # _20-90	user facility
NOS, an	d vasculiti	s. Outco	ome is unk	nown. *	12/09/1999	1	ND#	company representative
. Relevant tests/labor	atory data, including da	tes			6. If ND, protocol #	F	PLA#	distributor
						r	ore-1938	yes other
					7. Type of report	'	מזכ יייי	
					(check all that apply)	i	product	yes
					5-day 🔀 15-day	8.	Adverse event term	(s)
					10-day periodic	LI	VER FAILURE	, JAUNDICE,
					follow-up	#	LIRUBINEMIA	
					0 Aff wood gumber	PH	OSPHATASE I	NCREASED, VASCULITI
. Other relevant histo	ory, including preexists	ng medical condi sfunction, etc.)	tions (e.g., allergies	s, race pregnancy.	9. Mfr. report number			
					199922130HMRI			
NO MENT	ION OF RELE	VANT DIS	EASE		E. Initial report	e r		
					1. Name, address & phone #	l		
					JENNIFER SMITH PITT COUNTY MEMOI	DIAI. HOSP	TTAL _	
					PO BOX 6020	KIAL HOU!	DE	C 1 7 1999
					GREENVILLE, NC 2	7835 *		
	Cubmingin	n of a report	does not cons	stitute an				4. initial reporter also
FDA	admission	that medical	personnel, us	ser facility,	2. Health professional?	3. Occupat	uon	sent report to FDA
UA	distributor,	manufactur	er or product (caused or	yes no	1		yes no ur
main Factimae of	contributed item com	d to the even	it. tinuation pages					

chst Marion Roussel, Inc.

-	A. I. Patient Identifier	. G.9. Mfr. report number	
· ÆD WATCH		199922130HMRI	
			Page 2 of 2

B.2. Other outcome

medically important

B.5. Describe event or problem

[continuation:] Relevant medical history and relevant concomitant medications were not provided.

Reporter's assessment of causal relationship: Not provided.

Addendum 09-Dec-1999: A physician reported the diagnosis of hepatic failure. No other information was received.

Reporter's assessment of causal relationship: Not provided.

Reporter assessment of the causal relationship between the adverse ev	vent and suspect drug:
[_] Possible [_] Unlikely '[_] Unrelated	•
[_] Insufficient Data	
If unlikely/unrelated, provide alternative explanation:	
[_] Illness [_] Concomitant Drug [_] Other	

E.1. Name, address & phone

[continuation:] UNITED STATES 252-816-4257

DEC 2 0 1 3

Bert Burney

MedWatch Forms (USA)

UNK

(Dx) ACUTE HEPATOCELLULAR INJURY Reporter

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

2. Age at time of event:

Date of birth:

Adverse event or product problem

Patient information

Mospitalization - initial or prolonged

04/27/2002

Event (Nature of Event)

(Sx) ELEVATED AST (IN

(Sx) ELEVATED ALT (IN

(PEAK--9)

HEMOPTYSIS (Sx) DRY COUGH

6. Relevant tests/laboratory data, including dates

HYPERTENSION

(Sx) PULMONARY FIBROSIS (Sx) INTERSTITIAL INFILTRATES

(Sx) CHEMICAL HEPATITIS (Dx) INTERSTITIAL PNEUMONITIS

(Sx) INR--3.1

1000'S--PEAK 6000)

1000'S--PEAK 6000) (Sx) ELEVATED TOTAL BILIRUBIN

(Sx) BILIRUBIN INCREASED TO 22

SECONDARY TO SCLERODERMA (Sx) PRODUCTIVE COUGH WITH SOME

1. Patient identifier

in confidence

___ death __

3. Date of

life-threatening

5. Describe event or problem

1. Adverse event and/or

2. Outcomes attributed to adverse (check all that apply)

λG

Domain Facsimile	. Photog by PDR 01 3/22/9
Mfr report # 200214805US	
UF/Dist report #	
1	FDA Lies Con.

! ₹				 		
PORTING PROGR	LAM		Page 1 of 4	-		FDA Use
	*		C. Suspect med	ication(s)		
	J. Sex	4. Weight	Name (give labeled strength	& mfr/laheler if koo	turn)	
55 yrs	_ female	Ibs	#1 LEFLUNOMIDE (
NK	⊠ male	or kgs	#2 LEFLUNOMIDE ()	ARAVA) Table	ets	
oduct probl	em		2. Dose, frequency & route use			unknown, give duration)
	blem (e.g., defects	(malfunctions)	#1 20 MG QD PO	#1	from/to (or best estimate	e)
C,	(0.3., 00.000	- maneriolions;			· - 	
disabi	•		#2	#2	Duration	
	enital anomaly		4. Diagnosis for use (indication))	5.	Event abated after use stopp or dose reduced
	ed intervention to panent impairment/d		#1 SCLERODERMA		#1	
ged 🔲 other:			#2 SCLERODERMA			apply
			6. Lot # (if known)	7. Exp. date (if	known) #2	TIT YES TO WORD GOES!!
4. Date of this rep		2002	#1 UNK	#1	8.	Event reappeared after
(morday/yr)			#2 UNK	#2	1	reintroduction
•			9. NDC # - for product problems of		#1	L yes no doesn't
Event)	Dx O	rigin	#1	#2	#2	yes ☐ no ⊠ doesn't
CELLULAR I	NJURY Repo	rter	10. Concomitant medical produc	the and therapy date	n (ovelvets see se	annly
(IN			VERAPAMIL Unknown t			ent of event)
6000)			THE STATE OF THE C	.0 04/2//200	4	
(IN						
6000)						
AL BILIRUB	IN		G. All manufacture	ers		
			Contact office - name/address		evices)	2. Phone number
CREASED TO	22		Aventis Pharmaceutic		,	(908) 243 - 6000
			300 Somerset Corpora			
ATITIS			Bridgewater, NJ			3. Report source (check all that apply)
PNEUMONIT	IS Repor	rter	08807-2854			foreign
SCLERODERI	MA					study
OUGH WITH	SOME					literature
						consumer
						≟ health
ROSIS			Date received by manufacturer (moldaylyr)	5. (A)NDA # _	20-905	professional
INFILTRATE	ES	*	05/09/2002			user facility
lates			e Maio	ND# _		representative
			8. If IND, protocol#	PLA#_		distributor
				pre-1938	yes	other:
			7. Type of report (check all that apply)	отс	\Box	
				product	∟ yes	
		j	5-day 🛭 15-day	8. Adverse en	vent term(s)	
		1 1	10-day periodic	!		AGE, ASPARTATE
		1	🗵 Initial 🔲 follow-up #		NSFERASE I	
na madinal annativ	ne to a -it'			ALANINE	aminotrans	FERASE
ng medical condition function, etc.)	ns (e.g., allergies, raci		9. Mfr. report number		D, BLOOD B	
		1 1	200214805US	INCREASE	D, BLOOD B	ILIRUBIN *
	ER, NO KNOW	1	E. Initial reporter			
COHOL USE,	alcohol us	se T	1. Name, address & phone #			
			GUILLERMO GUZMAN MO		Γ	122
		, , ,	7502 GREENVILLE AVE		L	ZV, 71. 3
	MAY 2 4 2		SUITE 450		MAN	2 8 2002
		1 / 1	DALLAS. TX 75231 *		IV(A)	7 O / HU/

	GUIL	LERM
	7502	GRE

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or

2. Health professional? 3. Occupation 4. Initial reporter also sent report to FDA ≥ yes __ no Rheumatology ves по unk

contributed to the event ltem completed on continuation pages

Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy smoking and alcohol use, hepatic/renal dysfunction, etc.)

QUESTIONABLE COLLAGEN DISORDER, NO KNOWN DRUG ALLERGIES, ALCOHOL USE, alcohol use Aventis Pharmaceuticals, Inc.

MED WATCH

A.1. Patient identifier

G.9. Mfr. report number

200214805US

Pege 2 of 4

8.5. Describe event or problem

[continuation:]

(Dx) RIGHT-SIDED HEART FAILURE Reporter

(Sx) DILATED CARDIOMYOPATHY

(Sx) ALTERED MENTAL STATUS

(Sx) DECREASED EJECTION FRACTION (10%)

(Sx) CORONARY PLAQUES

(Dx) HEPATIC CONGESTION Reporter
SECONDARY TO R-SIDED HEART
FAILURE

(Sx) TOTAL BILIRUBIN (26MG/DL)

(Sx) INCREASED TRANSAMINASES IN

(Sx) INCREASED PT/INR

Narrative: Initial report 09-May-2002: This postmarketing case was reported by 2 different rheumatologists (prescribing physician and treating physician) via a sales representative. It involves a 55-year-old male patient receiving leflunomide 20mg daily since Feb 01 for scleroderma. He was given a loading dose of 100mg a day x 3 days. He consumed 1-2 alcoholic drinks/day while receiving Arava, as per the patient's wife. Concomitant medications include Verapamil, which was changed to Atenolol upon admission to the hospital on 27-Apr-2002. In Feb 2002, the patient started to experience dry cough which he was not treated for. In April 2002, 3 weeks prior to his admission to the hospital, he started to experience productive cough with hemoptysis. He was not treated for this event as vell. On 27-Apr-02, he was advised to go to the ER by the prescribing physician because the patient complained of a mild respiratory infection. In the ER, CXR revealed possible pneumonia, and he was admitted to the hospital. At this time, his LFT's were elevated (ALT and AST were both in 200's). Arava was discontinued. He was started on Levaquin (levofloxacin) 500mg PO once a day x 7 days. His respiratory condition progressively worsened. He had a complete work-up with ID, pulmonology, and GI consults (nos). His TB test was negative (patient travels). The results of the cultures are pending. Four days after the admission, patient was reported to be in liver failure with AST and ALT in the thousands with the peak of 6000, total bilirubin of 9 (peak), and INR of 3.1. On 01-May-2002, Arava washout procedure was started with cholestyramine 3 grams TID. He was seen by a Gastroenterologist who diagnosed him with chemical hepatitis secondary to Arava. Patient started to improve, and he was discharged home on 08-May-2002. He was discharged on Prednisone 60 mg once a day for the diagnosis of interstitial pneumonitis secondary to scleroderma. The treating physician reported that the patient recovered and not in liver failure as of 08-May-2002. As per the prescribing physician, patient's baseline LFT's were normal. He had regular LFT's (~every 2 months) performed, which were all normal. His last LPT's was 1-2 months prior to the hospital admission (normal).

Additional information from 13-May-2002 from the sales representative indicated the patient had leflunomide "washed out of his system" (NOS). The patient just left the hospital a couple of days ago.

Additional information from 14-May-2002: The patient's physician indicated the patient was discharged from the hospital on Thursday, 09-May-2002 with a bilirubin of 6.7. He was readmitted yesterday on 13-May-2002 with altered mental status and an alevated bilirubin of 22. The physician's causal assessment of the relationship between the suspected liver failure and Arava is related.

Additional information was received on 16-May-2002: According to the reporting rheumatologist, the patient has pure scleroderma, not rheumatoid arthritis. In the first hospital admission, the LFT's increased with maximum value of the ALT and AST in the 6000's (units not provided). The total bilirubin reached a maximum value of 9 mg/dl. A cholestyramine washout was done at 3 grams TID for a total of 13 days. During the hospitalization, the patient was diagnosed with interstitial lung disease, which was assessed to be compatible with Scleroderma Lung. The chest CT scan showed pulmonary fibrosis with interstitial infiltrates. At the time of his discharge from the first hospitalization, the patient's total bilirubin was 6.7 mg/dl and the transaminases were in the 300's. The patient's discharge medications included Prevacid, Atenolol and Prednisone.

At the time of the second hospital admission, the patient presented with altered mental status, and lab tests showed transaminases in the 300's and a total bilirubin of 26 mg/dl. The patient was found to be in right-sided heart ailure. An echocardiogram was done, and it showed dilated cardiomyopathy with ejection fraction of 10 consultant evaluated the patient and assessed the increased bilirubin level to be secondary to right-sided heart *



A.1. Patient Identifier

Aventis Pharmaceuticals, Inc.

MED WATCH

AG

G.9. Mfr. report number

200214805US

Page 3 of 4

B.5. Describe event or problem

(sontinuation) failure. The GI consultant relei out the diagnosis of liver failure; according to the GI specialist, the patient was not in liver failure. The GI consultant assessed that the abnormal liver function tests were associated with hepatic congestion secondary to right-sided heart failure, possible alcoholic liver disease and possible drug-induced hepatitis. It was revealed that the patient had a significant history of alcohol use. The etiology for the right-sided CHF has not been clearly established to date. It may be associated with the patient's pulmonary condition, the scleroderms lung. Also, the cardiomyopathy may be associated with the alcohol use. Furthermore, the high-resolution chest CT scan revealed plaques in the coronary arteries, suggestive of coronary artery disease. According to the GI consult, the possible drug-induced hepatitis appears to be associated with Arava therapy, not Levaquin. Liver biopsy was not done due to elevated PT and INR. According to the rheumatologist, the patient has pure scleroderms; there is no clinical evidence of rheumatoid arthritis. He does not believe the hepatitis to be autoimmune in nature. In terms of his current status, the patient is improving. The patient has recently been transferred out of the ICU. The patient's mental status and the LFT's, including PT/INR, are also improving.

Event (Dx) ACUTE HEPATOCELLULAR INJURY (Sx) BLEVATED AST (IN 1000'SPEAK 6000) (Sx) ELEVATED ALT (IN 1000'SPEAK 6000) (Sx) ELEVATED TOTAL BILIRUBIN (PEAK9)	Serious YES	Dechal NA	Rechal NA	Rpt.Causality Probable	Alternative Explanation other known or suspected cause
(Sx) BILIRUBIN INCREASED TO 22 (Sx) INR3.1 (Sx) CHEMICAL HEPATITIS (Dx) INTERSTITIAL PNEUMONITIS SECONDARY TO SCLERODERMA (Sx) PRODUCTIVE COUGH WITH SOME HEMOPTYSIS (Sx) DRY COUGH	YES	NA	N A		underlying/concomitant illness
(Sx) PULMONARY FIBROSIS (Sx) INTERSTITIAL INFILTRATES (Dx) RIGHT-SIDED HEART FAILURE (Sx) DILATED CARDIOMYOPATHY (Sx) ALTERED MENTAL STATUS (Sx) DECREASED EJECTION FRACTION (10%)	YES	NA	NA		underlying/concomitant illness
(Sx) CORONARY PLAQUES (Dx) HEPATIC CONGESTION SECONDARY TO R-SIDED HEART FAILURE (Sx) TOTAL BILIRUBIN (26MG/DL) (Sx) INCREASED TRANSAMINASES IN 300'S	YES	na :	NA		underlying/concomitant illness
Sx) INCREASED PT/INR					nee



Aventis Pharmaceuticals, Inc.

	A.1. Patient Identifier	G.9. Mfr. report number	
MED WATCH	AG	200214805US	
			Page 4 of 4

C.3. Therapy dates (if unknown, give duration) (mo/daylyr) (Suspect #1) * 02/??/2001 to 04/27/2002 Duration: 1 year 2 months

C.2. Dose, frequency & route used (Suspect #2)

100 (LOADING DOSE) MG QD PO

G.8. Adverse event term(s)

[continuation:] INCREASED, INTERNATIONAL NORMALISED RATIO INCREASED, HEPATITIS NOS, PNEUMONITIS NOS, HAEMOPTYSIS, COUGH, PULMONARY FIBROSIS, LUNG INFILTRATION NOS, CARDIAC FAILURE CONGESTIVE, CONGESTIVE (DILATED) CARDIOMYOPATHY, MENTAL STATUS CHANGES, EJECTION FRACTION DECREASED, CORONARY ARTERY DISEASE NOS, HEPATIC CONGESTION, BLOOD BILIRUBIN INCREASED, TRANSAMINASE NOS INCREASED, PROTHROMBIN TIME PROLONGED

E.1. Name, address & phone

[continuation:] UNITED STATES 214-691-3393

MAY 2 4 2002

DSS

MAY 2 8 2002

MedWatch Forms (USA)

entis Pharmaceuticals, Inc.

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THE FDA MEDICAL	PRODUCTS REPORT	ING PROGRAM

Page 1 of 6

Mfr report # 200215633US	
UF/Dist report #	
	FDA Use Only

	nformation	ú,			C. Suspect med	lication(s)	
Patient identifier	2. Age at time of event:	49 yrs	3. Sex	4. Weight	Name (give labeled strengt)		
CL	or		[female	lb:	s #1 LEFLUNONIDE (ARAVA) Tablets	
in confidence	Date 10/1	12/1952	Male male	or kg	s #2 INFLIXIMAB (R	EMICADE)	
B. Adverse	event or prod	uct proble	m	Company of			(If unknown, give duration)
1. 🖾 Adverse ever	nt and/or	1	em (e.g., defect	s/malfunctions	#1 20 NG QD PO	from to (or best estan	mie)
2. Outcomes attribute (check all that apply)					#2 QW PO		
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ife-threatening	(mordaylyr)		d intervention to p	orevent	#1 RHEUMATOID ART	· / •	 Event abated after use stop or dose reduced
		perman	ent impairment/c	amage		/*	H [] yes [] no [☑ does
nospitalizatio	n - initial or prolonged	f other: _			#2 RHEUMATOID ART		2 ves no does
Date of event		4. Date of	00/01/	2000	6. Lot#(if known)	7. Exp. date (if known)	apply
(maldey/yr)		this repor	08/01/	2002		*1	Event reappeared after reintroduction
. Describe event or pr	roblem	•			9. NDC # - for product problems	#2	1 🗌 yes 🗌 no 🔀 doesr
Event (1	Nature of Ev	ent)	Dx C	rigin	#1		apply
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(Dx) FUI	MINANT LIVE	R FAILURE			1 1	cts and therapy dates (exclude treat	ment of event)
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240	•				G. All manufactur	ere	
	REASED AST	(1000, 60	00,		Contact office - name/address		2. Phone number
200	- •				Aventis Pharmaceuti		(908) 243 - 6000
	REASED INR	(4.3, 2.4	,		300 Somerset Corpor	ate Blvd.	3. Report source
6.5 (Sx) WEA	•				Bridgewater, NJ 08807-2854		(check all that apply)
(Sx) FAT					08007-2054		foreign
	FUSION			İ			study
• -	EPHALOPATHY						literature
	Y PAIN						consumer health
· · · · · · · · · · · · · · · · · · ·	ST PAIN				4. Date received by manufacturer	5.	professional
(Sx) CHI					(ma/day/yr)	(A)NDA # 20-905	user facility
Relevant tests/laborate	pry data, including dates				07/24/2002	IND#	company
	ory data, including dates				6. If IND, protocol #	PLA #	representative
						pre-1938 ves	distributor
					7. Type of report	pre-1938 yes	other:
				ĺ	(check all that apply)	product yes	
					5-day 🔀 15-day	8. Adverse event term(s)	~
					10-day periodic	HEPATITIS ACUTE,	PPDATIC PATTOR
				ł	☐ Initial ☐ follow-up # 1	NAUSEA, VOMITING	NOS, ALANINE
Other relevant history.	including preexisting m	edical conditions	/a.n. allemias co		9. Mfr. report number	AMINOTRANSFERASE :	INCREASED,
imolding and alcohol use	e, hepatic/renal dysfunct	tion, etc.)	(a.g., анагую́в, гасс	r, pregnancy,	1	ASPARTATE AMINOTRA	
PPD POSTT	IVE, NO KNOW	יי מוזמת איי	מפירום מים זו		200215633US	INCREASED, INTERNA	ATIONAL *
nicotine		DRUG A	LABRULES,		E. Initial reporter		
	D ARTHRITIS,	HYPERTE	ISION		Name, address & phone #		
	DISK, QUEST			в.	ABLE TIELLO MD	DS	SS
	E ELEVATED L				420 DELAWARE SE MINNEAPOLIS, MN 55455		
	N, ANXIETY *				UNITED STATES 612-386	ALIC A C	2002
	Submission of a	report doce	not constitute				
$\square \Delta$	admission that i	medical perso	nnel, user fac	ility,			al reporter also
	distributor, man	ufacturer or p	product cause	d or	⊠ yes □ no		nt report to FDA Ses 20020 Z unk
Facsimile of	contributed to the	ge event.				, , p u <u>u</u>	yes Lyyto 🚣 unk

contributed to the event.
Item completed on continuation pages.



ventis Pharmaceuticals, Inc.

Domein Facsimile	Approved by F DA on 3/22/94
Mir report # 200215633UB	
JF/Dist report #	
	EDA US - O. I

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

C. SUSPECT MEDICATION(S) 1. Name (give labeled strength & minispecter, if known) 3. MSTHOTREXATE 44 METHOTREXATE 52 Dose, Prequency & route used graph of the strength of	Page 2 of 6		FDA Use
METHOTREXATE 4 METHOTREXATE 2 Dose, Prequency & route used graph of the provision of the	C. Suspect medic	ation(s)	
### METHOTREXATE 2. Dose, Prequency & route used ### 7.5 MG QW 4. Diagnosis for use (indication) ### 4. 4. Diagnosis for use (indication) ### 7.5 MG QW 4. Diagnosis for use (indication) ### 9			
2. Dose, frequency & route used #3 7.5 MG QW 44 5 MG QW 45 MG QW 45 S MG QW 46 Diagnosis for use (indication) #3 RIEUNATOID ARTHRITIS #4 REUNATOID ARTHRITIS #5 Lot # (if known) #6 REJUNATOID ARTHRITIS #6 REJUNATOID ARTHRITIS #7 Jesp. date (if known) #8 REJUNATOID ARTHRITIS #8 REJUNATOID ARTHRITIS #8 REJUNATOID ARTHRITIS #8 REJUNATOID ARTHRITIS #8 REJUNATOID ARTHRITIS #8 REJUNATOID ARTHRITIS #8 Lot # (if known) #8 Jesp. no does report consumer health professional user facility Jesp. no dees report consumer health professional user facility Type of report (check at that apply)	#3 METHOTREXATE		
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# IND # company representative distributor other: Type of report (check all that apply) 5-day	(mo/dey/yr)	1	
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yes no sent report to FDA		AU	U V ZUUZ
yes no sent report to FDA	Health professional? 3. Oc	cupation	4. Initial reporter also
AUG 0 5 2002 no - Junk	— —		sent report to FDA

Patient information 1. Patient identifier Age at time of event: 3. Sex 4. Weight CL [] female Date of birth: __ male in confidence kgs B. Adverse event or product problem 1. Adverse event and/or Product problem (e.g., defects/malfunctions) Outcomes attributed to adverse event (check all that apply) disability death _____ congenital anomaly required intervention to prevent life-threatening permanent impairment/damage hospitalization - initial or prolonged other: 3. Date of 4. Date of event (moldaylyr this report 5. Describe event or problem 6. Relevant tests/laboratory data, including dates Other resevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) Submission of a report does not constitute an

FDA
Domain Facsumile of

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.



entis Pharmaceuticals, Inc.

Domain Facalmile	Approved by FDA on 3/22/9
Mfr report # 20021563308	
UF/Olst report #	
	FDA Use Only

MEDYVAICH

THE FDA MEDICAL PI		TING PROGRA	м		Page 3 of 6			FDA Use
A. Patient info					C. Suspect me	edication(s)	
	Age at time of event:		3. Sex	4. Weight	Name (give labeled stren	gth & mfr/labeler	, if known)	
CT			female	Ibs	#5 ISONIAZID			
	Date of birth:		male	or kge	#6			
B. Adverse eve	ent or produ	ict proble	m		2. Dose, frequency & route	used	3. Therapy da	rtes (if unknown, give duration)
1. Adverse event as				cts/malfunctions	-		#5	l estimate)
2. Outcomes attributed to a	dverse event				7			
(check all that apply)		disabilit	•		4. Diagnosis for use (indicat		#6	
death	aylyt)	()	ital anomaly I intervention to		#5 PPD POSITIVE			Event abated after use stop or dose reduced
life-threatening		perman	ent impairment	/damage	3 110 10011178			#5 yes no does
hospitalization - in	itial or prolonged	other:	_		#6		_	apply
. Date of		4. Date of			6. Lot # (if known)	7. Exp. d	late (if known)	yes no doesn
event (modaylyr)		this report	l		#6	#5		Event reappeared after reintroduction
Describe event or probler	п	——————————————————————————————————————	•		#6	#6		
					9. NDC # - for product probler	ns only (if known	n)	#5 yes no doesn
					#5	#6		#6 yes no doesn
					10. Concomitant medical pro-	ducts and therap	v dates (exclude	Ireatment of event
								3. Report source (check all that apply) foreign study literature
					4. Date received by manufactur (modsylyt)		A#	consumer health professional user facility
Relevant tests/laboratory d	sta including dates					IND)#	
	n.cooking upics				6. If IND, protocol #	PLA	\#	representative
						pre-	-1938 🔲 ye	distributor
					7. Type of report	ОТО		es other;
					(check all that apply)	proc		es
				1	5-day 15-day	8. Adve	erse event term(s)
					10-day periodic			•
					☐ Initial ☐ follow-up #_			
Other relevant history, inclu	ding presisting me	rdical conditions	(e.g. allemine ::		9. Mfr. report number			
moking and alcohol use, he	patic/renal dysfuncti	on, etc.)	(-y., aserges, fa	ace, pregnancy.	o minimport indicat	!		
					E. Initial reporter			
					1. Name, address & phone #			100
							L	DSS
					ı			
							AUG	0 6 2002
e	Ibmission of -	ronord da-	mod com : 411	<u></u>				!
	ubmission of a	14h011 0062	not constitu	ra su	2. Health professional?			
ac ac	lmission that n stributor, man	nedical perso	onnel, user f	acility.	yes no	Occupation	4.	initial reporter also sent report to FDA

Submission of a report does not constitute ar admission that medical personnel, user facilit distributor, manufacturer or product caused of contributed to the event, item completed on continuation pages.

Health professional?	J. Occupation	4. Initial reporter also
ves no	İ	sent report to FDA
yes no		
	NIC O	2002 es _ no _
	AUG U	- 5005

Aventis Pharmaceuticals, Inc.

MED WATCH

A.1. Patient identifier

CL

G.9. Mfr. report number

200215633US

Page 4 of 6

B.5. Describe event or problem

[continuation:]

(Sx) COUGH

(Sx) DARK COLORED URINE

(Sx) OBTUNDED

(Sx) ABDOMINAL PAIN

(Sx) LOSS OF APPETITE

(Sx) SICKNESS

(Sx) JAUNDICE

(Dx) HYPOPHOSPHATEMIA

Reporter

(Dx) NEW LUNG LESION ON CHEST

Reporter

X-RAY

(Sx) SMALL BILATERAL PLEURAL EFFUSIONS

Narrative: Initial report: This spontaneous postmarketing case, received from a physician, involves a 49 year old Vietnamese male who initiated therapy with Arava (leflunomide) 20mg daily in early Apr-2002 for rheumatoid arthritis. It is not indicated if the patient received the loading dose of leflunomide. Leflunomide, methotrexate, Remicade (infliximab) and prednisone were discontinued on 20-May-2002 following his presentation to a clinic with jaundice. He did not undergo the cholestyramine washout. The patient had approximately 6 weeks of leflunomide therapy before it was discontinued. A chest x-ray done on 21-May-2002 revealed right upper lobe pleural thickening with possible parenchymal involvement, possibly a re-activation of tuberculosis. A previous chest x-ray done in vp-2001 was normal. On 22-May-2002 the patient presented to a local hospital with a one-week history of nausea and miting, generalized body pain, chest pain, fever, chills, cough, weak, tired, dark colored urine, abdominal pain, marked loss of appetite and sickness. He denied diarrhea and skin itching. On 22-May-2002 his ALT was 1841, AST was 1502, bilirunin was 1.4, BUN was 27, creatinine was 1.4, sodium was 134, potassium was 4.2, chloride was 99, CO2 was 27, anion gap was 8, hemoglobin was 16.6, and white count was 5.5. Urinalysis was positive for bilirubin, otherwise normal. Over the next 4 days the transaminases peaked around 6000 with an INR of 4.3. On 28-May-2002 the patient was transferred to another hospital. At that time his INR was 2.4, ALT was 2000 and AST was 2400. On 30-May-2002 the patient's INR peaked at 6.5. The patient underwent liver transplantation on 01-Jun-2002 and is currently recovering in the intensive care unit in stable condition. A renal ultrasound was done which was normal. No liver biopsy was done prior to the transplant. An abdominal ultrasound was done on 29-May-2002 which revealed the following: gallbladder appears ill defined with thickened walls with the suggestion of fluid within the walls, these changes may represent changes from hepatitis although cholecystitis cannot be excluded, liver is normal in echogenicity, (which can occur in the setting of hepatitis), unremarkable Doppler examination of the liver, small bilateral pleural effusions, and small amount of free fluid in the abdomen. The anatomic pathology of the liver and gallbladder revealed submassive necrosis of the liver and mild mucosal ischemic changes of the gallbladder. Section of the liver showed a proliferation of the bile ductules with small foci of hepatocytes with regenerative changes. These changes are consistent with a toxic insult. The following labs were provided:

	5/28	5/29	5/30	5/31	6/1	6/2	6/3	6/4	6/5	
ALT	2495	2685	1896	1294,518	596	560	46B	448	287	
Alk phos	189	256	186	163	137	112	95	110	88	
direct bili				0.2	0.5		0.3	0.3	0.2	
total bili CMV IgG Ab	11.0	14.4	13.2 123	13.8,7.4	3.0	1.2	0.9		0.9	DSS
EB, IgG		4.56								
Hgb	11.4		12.0		14.6,14.4,	13.3	13.2	14.6	13.5	AUG 0 6 2002
				10.2,9.5,	•					
				11.1,12.6,						
				14.3						

HBsAg was positive, total HAAb was positive, HAAb, IgM was negative, HBcAb total was positive and hepatitis B quant was 0.208.

ncomitant medications included methotrexate, infliximab, calcium, folate, and isoniarid for tuberculosis rophylaxis. Medical history is significant for rheumatoid arthritis, hypertension, borderline elevated liver *



ventis Pharmaceuticals, Inc.

	A.1. Patient Identifier	G.9. Mfr. report number	
MED WATCH	CL	200215633US	
	1		Page 5 of 6

B.5. Describe event or problem

[continuation:] function tests, depression, anxiety disorder and no known drug allergies.

Reporter's assessment of causal relationship: The patient was on 3 other medications that are known to be hepatotoxic, but the role of leflunomide cannot be ruled out.

Addendum for follow up received 24-Jul-2002: The following information was provided by the nurse: Patient is doing fair post transplant. His labs are much improved but is still experiencing a lot of pain and fatigue. The following labs from 05-Jul-2002 were provided: Alk phos=60 (40-150), ALT=<3 (0-70), AST=12 (0-55), conjugated bilirubin=0 (0-0.3), delta bilirubin=0 (0-0.4), total bilirubin=0.3 (0.2-1.3), urea nitrogen=17 (5-24), calcium=8.8 (8.2-10.4), chloride=102 (94-109), CO2 total=28 (20-32), creatinine=1.3 (0.8-1.5), glucose=250 (60-115), potassium=4.6 (3.4-5.3), sodium=138 (133-144), total protein=6.9 (6-8.2).

Event Serious Dechal Rechal Rpt.Causality Alternative Explanation Ox) ACUTE HEPATITIS YES UNK UNK Possible (Dx) FULMINANT LIVER FAILURE YES UNK UNK Possible (Sx) NAUSEA (Sx) VOMITING (Sx) INCREASED ALT (1500. 6000, 2400) (Sx) INCREASED AST (1000, 6000, 2000) (Sx) INCREASED INR (4.3, 2.4, 6.5) (Sx) WEARNESS (Sx) FATIGUE (Sx) CONFUSION (Sx) ENCEPHALOPATHY

possibly associated with concomitant drug(s) possibly associated with concomitant drug(s)

underlying/concomitant illness

AUG 0 6 2002

(8x) ABDOMINAL PAIN (Sx) LOSS OF APPETITE

(Sx) DARK COLORED URINE

(Sx) SICKNESS

(Sx) OBTUNDED

(Sx) BODY PAIN (8x) CHEST PAIN (Sx) CHILLS (Sx) COUGH

(Sx) JAUNDICE

(Dx) HYPOPHOSPHATEMIA NA NA

(Dx) NEW LUNG LESION ON CHEST X-RAY YES NΑ

(Sx) SMALL BILATERAL PLEURAL

EFFUSIONS

Nλ underlying/concomitant illness

^{*.} Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.) continuation: | Race: ASIAN



entis Pharmaceuticals, Inc.

MED WATCH

A.1. Patient Identifier

G.9. Mfr. report number

200215633UB

Page 6 of 6

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #1)

04/??/2002 to 05/20/2002 Duration: 6 weeks

C.3. Therapy dates (if unknown, give duration) (mo/day/yr) (Suspect #4)

04/08/2002 to 05/20/2002 Duration: 6 weeks 1 day

G.8. Adverse event term(s)

[continuation:] NORMALISED RATIO INCREASED, WEAKNESS, FATIGUE, CONFUSION, ENCEPHALOPATHY NOS, PAIN NOS, CHEST PAIN, RIGORS, COUGH, CHROMATURIA, DEPRESSED LEVEL OF CONSCIOUSNESS, ABDOMINAL PAIN NOS, ANOREXIA, ILL-DEFINED DISORDER NOS, JAUNDICE NOS, HYPOPHOSPHATAEMIA, LUNG DISORDER NOS, PLEURAL EFFUSION

DSS AUG 0 6 2002